10-20-09

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re U.S. Patent No. 5,380,936)
)
Issued: January 10, 1995)
)
To: Commissioner of Patents)
)
Assignee: Lundbeck Inc.)
)
For: Process for Preparing 4-Amino-5-Hexenoic Acid)

ATTN: MAIL STOP PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Application for extension of patent term pursuant to 35 U.S.C. § 156

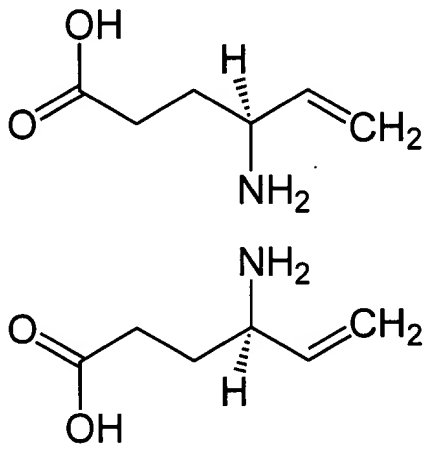
Applicant, Lundbeck Inc. represents that it is the Assignee of the entire interest in and to U.S. Patent No. 5,380,936 granted to Patrick Casara by virtue of an assignment from the inventor to Merrell Dow Pharmaceuticals Inc., recorded in the U.S. Patent and Trademark Office at Reel 020497 Frame 0674 on February 13, 2008, and from Merrell Pharmaceuticals, Inc. to Ovation Pharmaceuticals, Inc. recorded in the U.S. Patent and Trademark Office at Reel 014475 Frame 0329 on March 31, 2004. Lundbeck Inc. is the successor in interest to Ovation Pharmaceuticals, Inc. recorded in the U.S. Patent and Trademark Office at Reel 023163 Frame 0803 on September 1, 2009. By the Power of Attorney enclosed herein (Attachment A), applicant appoints several individuals as attorneys for Lundbeck Inc. with regard to this application for

extension of the term of U.S. Patent No. 5,380,936 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Information Required Under 37 C.F.R. § 1.740

Applicant hereby submits this application for extension of the patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For convenience, the information will be submitted in the format which follows the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

1) The approved product is branded Sabril®, generically known as vigabatrin ((RS)-4-aminohex-5-enoic acid), and exists as the two enantiomers below:



Sabril® is available in a 500mg tablet form and as 500mg powder for oral solution.

2) The approved product was subject to regulatory review under Section 505 of the Federal Food, Drug and Cosmetic Act.

3) Sabril® received FDA approval for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on August 21, 2009.

Copies of the approval letters for NDA 20-427 and NDA 22-006 are attached (Attachment B).

4) The active ingredient in Sabril® is vigabatrin which, on information and belief, has not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of either NDA 20-427 or NDA 22-006 by the Food and Drug Administration on August 21, 2009. A copy of the package insert describing the approved product is attached (Attachment C).

5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f), said period will expire on October 20, 2009.

6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventor: Patrick Casara

Patent No.: 5,380,936

Filing Date: January 19, 1994, claiming benefit of application filed December 7, 1992

Issue Date: January 10, 1995

Expiration Date: December 7, 2012

7) A true copy of the patent is attached (Attachment D)

8) No reexamination certificate has been issued on this patent. A copy of a certificate of correction is attached to Attachment D. Copies of records of maintenance fee payments under 35 U.S.C. § 41(b) are attached (attachment E)

9) U.S. Patent No. 5,380,936 claims a process of preparing 4-Amino-5-Hexenoic Acid. Claim 1 is the applicable patent claim directed to a method of manufacturing vigabatrin (a.k.a. 4-Amino-5-Hexenoic Acid) which is the active ingredient in the approved product. The following description demonstrates the manner in which at least one claim reads on a method of manufacturing the approved product.

Claim 1 reads as follows: The process for preparing 4-amino-5-hexenoic acid, or its pharmaceutically acceptable salts thereof which comprises the steps:

(a) thermally rearranging erythritol to 4-formyloxy-3-hydroxy-1-butene, in the presence of an excess of formic acid,

(b) thermally rearranging 4-formyloxy-3-hydroxy-1-butene to ethyl 6-formyloxy-4-hexanoate, followed by the conversion of the formate to its corresponding alcohol ethyl 6-hydroxy-4-hexanoate,

(c) converting the so-produced ethyl 6-hydroxy-4-hexanoate to ethyl 6-trichloroacetimidoxy-4-hexanoate by reaction with trichloroacetonitrile, followed by its thermal rearrangement to ethyl-4-trichloroacetamido-5-hexanoate which, by hydrolysis is converted to the desired 4-amino-5-hexenoic acid, and optionally converting said acid to a pharmaceutically acceptable salt thereof.

This claim reads on a method of manufacturing 4-amino-5-hexenoic acid, the IUPAC nomenclature for vigabratrin, the active ingredient of Sabril®.

10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

Investigational New Drug Application (IND 17213) for Sabril® (vigabatrin) was submitted to the FDA on February 15, 1980 and became effective on September 14, 1981.

New Drug Application for Sabril® NDA 20-427 was submitted on April 29, 1994, and NDA 22-006 was submitted on October 17, 2006

New Drug Applications for Sabril® (NDA 20-427 and NDA 22-006) were both approved on August 21, 2009.

11) A compilation of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to Sabril® and the dates applicable to these significant activities are set forth in the chronology of events attached (Attachment F).

12(a)(i) It is the Applicant's opinion that U.S. Patent 5,380,936 is eligible for extension of the patent term under 35 U.S.C. § 156 because is satisfies all requirements for such extension as follows:

a) 35 U.S.C. § 156(a) – U.S. Patent 5,380,936 claims a method of manufacturing vigabatrin, the active ingredient in Sabril®.

b) 35 U.S.C. § 156(a)(1) – U.S. Patent 5,380,936 has not expired before the submission of this application.

(c) 35 U.S.C. § 156(a)(2) – The term of U.S. Patent 5,380,936 has never been extended under35 U.S.C. § 156(e)(1).

d) 35 U.S.C. § 156(a)(3) – The application for patent term extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

e) 35 U.S.C. § 156(a)(4) – The product Sabril® has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) – The commercial marketing or use of Sabril® after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug and Cosmetic Act (i.e., Section 505) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4) – No other patent has been extended for the same regulatory review period for the product Sabril®.

12(a)(ii) Applicant respectfully submits that the length of the extension of patent term for U.S. Patent 5,380,936 is 5 years pursuant to 37 C.F.R. § 1.775, calculated as follows:

a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on September 14, 1981 and ended August 21, 2009, which is a total of 10,204 days, which is the sum of 1 and 2 below.

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period", began on September 14, 1981 and ended on April 29, 1994, which is 4,610 days; and

(2) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Approval Period", began on April 29, 1994 and ended on August 21, 2007, which is 5,594 days.

b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(ii)(a) above (10,204) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (January 10, 1995) which is 4,871 days; and

(2) The number of days in the regulatory review period in which applicant did not act with due diligence, which is 0 days; and

(3) One half the number of days determined in subparagraph (12)(ii)(a)(1) above after the patent issued (one-half of 0) is 0 days.

c) The number of days as determined in subparagraph (12)(ii)(b) (10,204 – 4,871 – 0 – 0 = 5,333) when added to the original term of the patent (December 7, 2012) would result in the expiration date of July 15, 2027.

d) Fourteen years when added to the date of the NDA approval (August 21, 2009) results in a date of August 21, 2023.

(e) The earlier date as determined in subparagraphs (12)(ii)(c) and (12)(ii)(d) is August 21, 2023.

(f) Since U.S. Patent No. 5,380,936 issued after September 24, 1984, the period of extension may not exceed five years from the original expiration date of December 7, 2012. Five years added on to the original expiration date of the patent results in an expiration date of December 7, 2017.

(g) The earlier date as determined by subparagraphs (12)(ii)(e) and (12)(ii)(f) is December 7, 2017.

13) Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

14) The prescribed fee for receiving and acting upon this application is $1,120.00. Director is authorized to charge the prescribed fee and any additional fees required by this application to Deposit Account No. 23-0920.

15) All correspondence and inquiries may be directed to the undersigned, whose address, phone and fax numbers appear below:

Edward P. Gamson, Reg. No. 29,381

HUSCH BLACKWELL SANDERS WELSH & KATZ, LTD.
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60606
Phone (312) 655-1500
Fax No. (312) 655-1501

16) Enclosed is a certification that the application for extension of patent term under 35 U.S.C. § 156, including its attachments and supporting papers is being submitted as one original and two copies thereof (Attachment G)

Respectfully submitted,

By: 
Edward P. Gamson
Reg. No. 29,381

Counsel for Lundbeck, Inc.

Date: October 19, 2009

Attachments:

Transmittal Letter
Power of Attorney (Attachment A)
FDA Approval Letters (Attachment B)
Package Inserts for Sabril® (Attachment C)
U.S. Patent No. 5,380,936 (Attachment D)
Maintenance Fees Paid (Attachment E)
Chronology of Approval (Attachment F)
Certification of Copies of Application Papers (Attachment G)

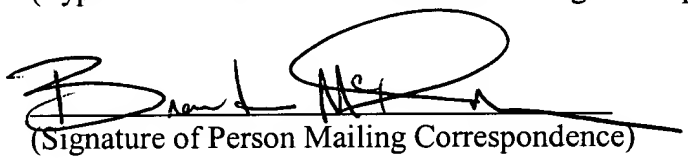
CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): Patrick Casara Assignee: Lundbeck Inc.			Docket No. (4458/105720)
In re U.S. Patent No. 5,380,936	Issue Date January 10, 1995	Primary Examiner Michael L. Shippen	Prior Group Art Unit: N/A

Title: PROCESS FOR PREPARING 4-AMINO-5-HEXENOIC ACID

[ORIGINAL OF ALL DOCUMENTS AND 2 COPIES OF DOCUMENTS]
Transmittal Letter,
Application for Extension of Patent Term Pursuant to 35 U.S.C. §156,
Power of Attorney (Attachment A),
FDA Approval Letters (Attachment B),
Package Inserts for Sabril® (Attachment C),
U.S. Patent No. 5,380,936 (Attachment D),
Maintenance Fees Paid (Attachment E),
Chronology of Approval (Attachment F),
Certification of Copies of Application Papers (Attachment G),
Fee in the amount of $1,120.00 for Extension of Patent Term, charged to Deposit Account No. 23-0920, and Return Postcard.

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: Mail Stop Patent Extension, Commissioner for Patents, PO Box 1450, Alexandria, Virginia 22313-0001 on October 19, 2009.

Brandon McKinnon
(Typed or Printed Name of Person Mailing Correspondence)


(Signature of Person Mailing Correspondence)

EV731141427US
("Express Mail" Mailing Label Number)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re U.S. Patent No. 5,380,936	)	Patent
	)	
Issued: January 10, 1995	)	
	)	
To: Commissioner of Patents	)	
	)	
Assignee: Lundbeck Inc.	)	
	)	
For: Process for Preparing 4-Amino-5-Hexenoic Acid	)	

ATTN: MAIL STOP PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 AND 37 C.F.R. §1.740

Submitted herewith is one original and two copies of an application for extension of patent term of the above-identified patent pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.740, and its stated enclosures.

The Commissioner is hereby authorized to charge the fee of $1120 under 37 C.F.R x1.20(j) and any other fee that may be required for receiving and acting upon the accompanying application for extension to Deposit Account No. 23-0920. A duplicate copy of this letter is enclosed.

Respectfully submitted,

Date: October 19, 2009

Edward P. Gamson
Reg. No. 29,381

HUSCH BLACKWELL SANDERS WELSH & KATZ, LTD.
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60606
Phone (312) 655-1500
Fax No. (312) 655-1501

Attachment A

[Power of Attorney]

PTO/SB/81A (12-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	5,380,936
Issue Date	January 10, 1995
First Named Inventor	Patrick Casara
Title	PROCESS FOR PREPARING 4-AMINO-5-HEXENOIC ACID
Attorney Docket Number	

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 24628

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature	Charles R. Krikorian	Date	10/19/09
Name	Charles R. Krikorian, Ph.D., J.D.	Telephone	847-282-5778
Title and Company	Vice-President of Lundbeck Inc.		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Attachment B

[FDA Approval Letters]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-427

NDA APPROVAL

Lundbeck Inc.
Attention: Jenny Swalec, Sr. Director
Global Regulatory Affairs
4 Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your new drug application (NDA) dated April 29, 1994, received May 2, 1994, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (vigabatrin) Tablets, 500 mg.

Reference is also made to the Agency's Not Approvable Letter dated April 28, 1995, Approvable Letter dated November 26, 1997, and Not Approvable Letter dated October 27, 1998.

We acknowledge receipt of your additional correspondence and amendments dated:

December 28, 2007	February 11, 2008	February 12, 2008	March 14, 2008
April 10, 2008	April 15, 2008	April 23, 2008	April 25, 2008
May 2, 2008	May 6, 2008	May 7, 2008	May 14, 2008
May 15, 2008	May 16, 2008	May 23, 2008	May 27, 2008
May 29, 2008	June 2, 2008	June 2, 2008	June 4, 2008
June 6, 2008	June 6, 2008	June 11, 2008	June 18, 2008
June 20, 2008	June 26, 2008	June 30, 2008	July 23, 2008
July 25, 2008	August 4, 2008	October 31, 2008	November 21, 2008
November 24, 2008	November 24, 2008	November 26, 2008	December 24, 2008
January 12, 2009	January 30, 2009	February 5, 2009	February 5, 2009
February 12, 2009	February 19, 2009	February 24, 2009	March 10, 2009
March 25, 2009	April 2, 2009	April 9, 2009	April 21, 2009
April 30, 2009	June 22, 2009	July 7, 2009	July 14, 2009
July 29, 2009	August 18, 2009		

The December 28, 2007, submission constituted a complete response to our October 27, 1998, action letter.

This new drug application provides for the use of Sabril (vigabatrin) Tablets for Refractory Complex Partial Seizures in Adults.

We have completed our review of this application, as amended and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to 10 years because necessary studies are impossible or highly impracticable. Evidence strongly suggests that Sabril (vigabatrin) would be unsafe in this pediatric group. The visual toxicity of Sabril would be difficult to monitor in children 10 years of age and younger and other drugs are available to treat complex partial seizures, even refractory seizures. Thus, any possible benefit of Sabril (vigabatrin) used in this population appears to be clearly outweighed by its risks.

We are deferring the requirement for pediatric studies for ages 10 to 16 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study, required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act, is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required study is listed below:

1526-1: Deferred pediatric study under PREA for the treatment of Refractory Complex Partial Seizures in pediatric patients ages 10 to 16.

The study is to be a multi-center, randomized, placebo-controlled double blind parallel-design study evaluating the safety and efficacy of several fixed doses of Sabril (vigabatrin) as adjunctive therapy in pediatric patients age 10 years and above with refractory complex partial seizures. Adequate visual monitoring and stopping rules must be incorporated into this study.

Protocol Submission Date:	by October 2009
Study Completion Date:	by January 2014
Final Report Submission:	by April 2014

Submit final study reports to this NDA. Use the following designator to prominently label all submissions:

"**Required Pediatric Assessment(s)**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Assess the known serious risk of vision loss with Sabril (vigabatrin) and the potential mechanisms for mitigating the vision loss.
- Identify the unexpected serious risk for Sabril (vigabatrin) to induce CYP1A2 and CYP3A4 enzymes. Induction of these enzymes could result in the loss of effect of antiepileptic and other drugs that are metabolized by these enzymes, and therefore could increase the risk of adverse outcomes including seizures.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1526-2: A study analyzing data from the Registry provided for in the REMS to evaluate the development of visual lesions, timing and risk of the development of concentric field loss, the risk of visual acuity deficits, the potential for progression of the lesions if therapy is continued, and the potential for progression once therapy has been discontinued.

Final Protocol Submission:	by August 2009
Study Completion Date:	by July 2016
Final Report Submission:	by September 2016

1526-3: A study examining the protective effect of taurine on vigabatrin-induced retinal damage in rodents, as reported by Jammoul *et al.* (Jammoul A F *et al. Ann Neurol* 65:98-107, 2009), but administering vigabatrin by the oral route. An attempt should be made to induce retinal toxicity in pigmented animals by, for example, exposing them to high intensity light for an appropriate duration following induction of mydriasis (cf. Rapp LM, Williams TP *Vision Res* 20:1127-1131, 1980). If this is successful, the study should be conducted in both albino and pigmented animals. The final study protocol should be submitted to the Agency for comment prior to study initiation.

Final Protocol Submission:	by January 2010
Study Completion Date:	by June 2011
Final Report Submission:	by November 2011

1526-4: An *in vitro* study to evaluate the ability of Sabril (vigabatrin) to induce CYP1A2 and CYP3A4 using methods described in the FDA Guidance for Industry: Drug interaction studies: Study Design, Data Analysis and Implications for Dosing and Labeling.

Protocol Submission:	by September 2009
Study Completion Date:	by April 2010
Final Report Submission:	by May 2010

Submit the protocol to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Sabril (vigabatrin) to ensure the benefits of the drug outweigh the risks of vision loss and of suicidal thoughts and behaviors.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Sabril (vigabatrin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Sabril (vigabatrin). FDA has determined that

Sabril (vigabatrin) is a product for which patient labeling could help prevent serious adverse effects. Sabril also has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect their decisions to use, or continue to use, Sabril (vigabatrin). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Sabril (vigabatrin).

We have also determined that a communication plan is necessary to support implementation of the REMS. The communication plan should be implemented at product launch (the first six months after product approval) and continued for three years.

Pursuant to 505-1(f)(1), we have also determined that Sabril (vigabatrin) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate these risks listed in the labeling. The elements to assure safe use will mitigate the risk of Sabril (vigabatrin)-induced vision loss by ensuring that patients receive appropriate monitoring of vision, and by ensuring that Sabril (vigabatrin) therapy is discontinued in patients who experience inadequate clinical response.

Your proposed REMS, submitted on August 18, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS Assessment Plan should include, but is not limited to, the following:

1) Registration and drug distribution data

2) Medication Guide assessment data
   a) Patients' understanding of the serious risks of Sabril (vigabatrin)
   b) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
   c) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

3) Report of mandatory benefit-risk assessments prior to entering maintenance therapy, including how many patients completed the mandatory benefit-risk assessment, and how many patients did not complete the mandatory benefit-risk assessment.

4) Vision Monitoring

5) Patient/Parent or Legal Guardian Knowledge, Attitude and Behavior (KAB) Surveys

6) Ophthalmic professional KAB Surveys

7) Prescriber KAB Surveys

Additional details for the REMS assessment plan are in Appendix I.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

The requirements for assessments of an approved REMS also include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 20-427 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 20-427
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 20-427
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 20-427."

IMMEDIATE CONTAINER LABELS

Submit final printed container labels that are identical to immediate container labels submitted on June 22, 2009 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Container Labels for approved NDA 20-427." Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Tamy Kim, PharmD, Senior Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Appendix I, Labeling and REMS

Appendix I: REMS Assessment Plan

1) Registration and drug distribution data
   a) Report of Sabril® (vigabatrin) distribution;
   b) The number of patients registered for the reporting period and cumulatively, including the age and gender of the patients;
   c) The number and specialties of prescribers registered for the reporting period and cumulatively;
   d) The number of patients who discontinue Sabril® (vigabatrin) therapy before the beginning of the maintenance phase;
   e) The number of patients whose therapy is interrupted because of changing prescribers.
   f) The number of prescribers who are de-registered and reasons;
   g) The number of prescribers who are re-registered and reasons;
   h) The number of patients who are de-registered and reasons;
   i) The number of Sabril® (vigabatrin) shipments to patients without prior authorization from Lundbeck Inc.; and
   j) The number of pharmacies who are de-enrolled, with reasons for de-enrollment.

2) Medication Guide assessment data
   a) Patients' understanding of the serious risks of Sabril (vigabatrin)
   b) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
   c) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

3) Report of mandatory benefit-risk assessments prior to entering maintenance therapy, including how many patients completed the mandatory benefit-risk assessment, and how many patients did not complete the mandatory benefit-risk assessment.

4) Vision Monitoring
   a) Frequency distribution of number of reminder calls for vision monitoring made per patient;
   b) Review of pattern of reminder calls to confirm no gap in therapy;
   c) The number of patients who miss vision monitoring appointments, the reason they miss them, and how long the monitoring is delayed;
   d) The number and percent of patients who obtain baseline vision monitoring within the first 2 weeks and within the first 4 weeks of treatment initiation, age, and prescriber;
   e) The number and percent of patients who do not obtain baseline vision monitoring within the first 4 weeks after treatment initiation, by reason, age, and prescriber;
   f) The number of patients who are at least 60 days late in obtaining required vision monitoring appointments on 3 separate occasions;
   g) The number of patients by age who do not complete the required vision monitoring within the REMS assessment period;

h) The number of patients who are exempted from vision monitoring by reason checked on the Ophthalmologic Assessment Form and by prescriber;
i) Narrative summary and analysis of information collected on Ophthalmologic Assessment Forms; and
j) Narrative summary and assessments of reports of vision loss.

5) Patient/Parent or Legal Guardian Knowledge, Attitude and Behavior (KAB) Surveys
   a) Number of patients, parents, and legal guardians who call to volunteer for survey participation;
   b) Number of patients who meet inclusion criteria;
   c) Description of survey participants;
      i) Indication for Sabril (vigabatrin) use;
      ii) Duration of use (as indicated in SHARE database);
      iii) Gender;
      iv) Age;
      v) Geographic region;
      vi) Status (patient, parent, legal guardian); and
      vii) Where treated.
   d) Frequency distribution of responses to each question; that is, the number of respondents who give each answer to each question;
   e) Percent of those answering each response to each question in total and separately for patients and caregivers;
   f) Percent of respondents indicating correct response to each objective in total and separately for patients and caregivers;
   g) Analyses will be stratified by indication for Sabril (vigabatrin) use as well as analyses for the combined sample;
   h) Level of understanding of Sabril (vigabatrin) risks as measured by the score on the KAB survey;
   i) Number and percent of respondents in patient/parent/legal guardian KAB survey who report reading the Medication Guide; and
   j) Number and percent of respondents in the patient/parent/legal guardian KAB survey who report they receive a Medication Guide with each prescription.

6) Ophthalmic professional KAB Surveys
   a) The number of ophthalmic professionals in the sample, in total, and by key characteristics;
   b) The number of ophthalmic professionals that you attempted to contact at each wave; of those you attempted to contact:
      i) number who opt out/ask to be removed from list;
      ii) number who agree to participate in the survey;
      iii) Of those who agree to participate, number who qualify;
      iv) Of those who qualify, number who complete any portion of the interview; and

v) Of those who qualify, number who complete the survey.

c) Description of survey participants
   i) Experience with Sabril (vigabatrin); and
   ii) Geographic region.
d) Frequency distribution of responses to each question;
e) Percent of those answering each response to each question; and
f) Percent of respondents indicating correct response to each objective.

7) Prescriber KAB Surveys
   a) The number of physicians in the sample, in total, and by key characteristics;
   b) The number of physicians attempted to contact at each wave; of those attempted to contact:
      i) Number who opt out/ask to be removed from list;
      ii) Number who agree to participate in the survey;
      iii) Of those who agree to participate, number who qualify;
      iv) Of those who qualify, number who complete any portion of the interview;
      v) Of those who qualify, number who complete the survey;
      vi) Description of survey participants;
         (1) Medical specialty & whether adult or pediatric practice;
         (2) Experience with Sabril (vigabatrin); and
         (3) Geographic region.
      vii) Frequency distribution of responses to each question;
      viii) Percent of those answering each response to each question; and
      ix) Percent of respondents indicating correct response to each objective; and
   c) Additional analyses, included subset by adult or pediatric practice, if needed.

FDA-approved labeling 8/21/09

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SABRIL safely and effectively. See full prescribing information for SABRIL.

SABRIL® (vigabatrin) Tablets
For Oral Administration Only
Initial U.S. Approval: Pending

℞ **Only**

WARNING: VISION LOSS
See full prescribing information for complete boxed warning

- SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity.
- Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss
- Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL
- Periodic vision testing is required for patients on SABRIL, but cannot reliably prevent vision damage
- Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program

----------INDICATIONS AND USAGE----------

SABRIL is an antiepileptic drug (AED) indicated for:

- **Refractory Complex Partial Seizures in Adults** (1.1). It should be used as adjunctive therapy in patients who have responded inadequately to several alternative treatments.

----------DOSAGE AND ADMINISTRATION----------

- Refractory Complex Partial Seizures in Adults: Initiate therapy at 500 mg twice daily, increasing total daily dose per instructions. The recommended dose is 1.5 grams twice daily (2.1).
- Dose adjustment recommended in renally impaired patients (2.2)
- Reduce dose gradually upon discontinuation (2.3)

----------DOSAGE FORM AND STRENGTHS----------

Tablet: 500 mg (3.1)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- SABRIL causes permanent vision loss (5.1)
- Abnormal MRI signal changes have been reported in some infants with IS receiving SABRIL (5.3)
- Antiepileptic drugs, including SABRIL, increase the risk of suicidal thoughts and behavior (5.5)
- Dose should be tapered gradually to avoid withdrawal seizures (5.6)
- SABRIL causes anemia (5.7)
- SABRIL causes somnolence and fatigue (5.8)
- SABRIL causes peripheral neuropathy (5.9)
- SABRIL causes weight gain (5.10)
- SABRIL causes edema (5.11)

----------ADVERSE REACTIONS----------

Most common adverse reactions (change of ≥5% over placebo) in addition to permanent vision loss in adult controlled trials with vigabatrin were fatigue, somnolence, nystagmus, tremor, vision blurred, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck Inc. at 1-800-455-1141 or www.lundbeckinc.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Decreased phenytoin plasma levels have been reported (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available (8.1)
- Nursing Mothers: SABRIL is excreted in human milk (8.2)
- Renal Impairment: Dose adjustment recommended (2.2, 8.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

Issued: 08/07/09

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: VISION LOSS

- SABRIL causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss
- Vision testing at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy is required for adults on SABRIL. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. Once detected, vision loss due to SABRIL is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.
- It is possible that vision loss can worsen despite discontinuation of SABRIL
- Because of the risk of vision loss, SABRIL should be withdrawn from patients who fail to show substantial clinical benefit within 3 months of initiation, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.
- Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient, can still adversely affect function.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks
- The lowest dose and shortest exposure to SABRIL should be used that is consistent with clinical objectives

Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program called SHARE, by calling 1-888-45-SHARE. Only prescribers and pharmacies registered with SHARE may prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE [*see* WARNINGS AND PRECAUTIONS, Distribution Program for SABRIL (5.2)].

1 INDICATIONS AND USAGE

1.1 Refractory Complex Partial Seizures in Adults

SABRIL® is indicated as adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of

vision loss [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)]. SABRIL is not indicated as a first line agent for complex partial seizures.

2 DOSAGE AND ADMINISTRATION

2.1 Refractory Complex Partial Seizures in Adults

SABRIL 500 mg tablets should be given as twice daily oral administration with or without food. Therapy should be initiated at 1 g/day (500 mg twice daily). Total daily dose may be increased in 500 mg increments at weekly intervals depending on response. The recommended dose of SABRIL in adults is 3 g/day (1.5 g twice daily). A 6 g/day dose has not been shown to confer additional benefit compared to the 3 g/day dose and is associated with an increased incidence of adverse events.

2.2 Patients with Renal Impairment

SABRIL is primarily eliminated through the kidney. In patients with renal impairment, dose adjustments should be made as follows:

In patients with mild renal impairment (CLcr >50 to 80 mL/min), the dose should be decreased by 25%; in patients with moderate renal impairment (CLcr >30 to 50 mL/min), the dose should be decreased by 50%; and in patients with severe renal impairment (CLcr >10 to <30 mL/min), the dose should be decreased by 75%.

CLcr in mL/min may be estimated from a serum creatinine (mg/dL) determination using the following formula:

CLcr *= [140-*age* (*years*)] *weight* (*kg*)/72 *serum creatinine* (*mg/dL*)]
*[0.85 *for female patients*]

The effect of dialysis on SABRIL clearance has not been adequately studied.

[see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5)].

2.3 General Dosing Considerations

SABRIL should be withdrawn gradually. In controlled clinical studies in adults with CPS, vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6)].

3 DOSAGE FORMS AND STRENGTHS

3.1 Tablet

500 mg Tablet.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Vision Loss (see BOXED WARNING)

Because of the risk of vision loss and because SABRIL, when it is effective, provides an observable symptomatic benefit, a patient who fails to show substantial clinical benefit within 3 months of initiation of treatment, should be withdrawn from SABRIL. If in the clinical judgment of the prescriber evidence of treatment failure becomes obvious earlier than 3 months, treatment with SABRIL should be discontinued at that time. Patient response to and continued need for treatment should be periodically assessed.

Monitoring of Vision

Monitoring of vision by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina is required. Vision testing at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months is required for adults on SABRIL. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.

The diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor vision periodically must be documented under the SHARE program. Perimetry is recommended, preferably by automated threshold visual field testing. Additional testing may also include electrophysiology (e.g., electroretinography [ERG]), retinal imaging (e.g., optical coherence tomography [OCT]), and/or other methods appropriate for the patient. In patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate patient counseling and with documentation in the SHARE program of the inability to test vision. Because of variability, results from ophthalmic monitoring must be interpreted with caution, and repeat testing is recommended if results are abnormal or uninterpretable. Repeat testing in the first few weeks of treatment is recommended to establish if, and to what degree, reproducible results can be obtained, and to guide selection of appropriate ongoing monitoring for the patient.

The onset and progression of vision loss from SABRIL is unpredictable, and it may occur or worsen precipitously between tests. Once detected, vision loss due to SABRIL is not reversible. It is expected that even with frequent monitoring, some SABRIL patients will develop severe vision loss.

5.2 Distribution Program for SABRIL

SABRIL is available only under a special restricted distribution program called the SHARE program. Under the SHARE program, only prescribers and pharmacies registered with the program are able to prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE. Contact the SHARE program at 1-888-45-SHARE.

To enroll in SHARE, prescribers must understand the risks of SABRIL and complete the SHARE Prescriber Enrollment and Agreement Form indicating agreement to:

- Enroll all patients in SHARE
- Review the SABRIL Medication Guide with every patient
- Educate patients on the risks of SABRIL, including the risk of vision loss [see BOXED WARNING: VISION LOSS]
- Order and review vision assessments at initiation of SABRIL treatment and every 3 months during therapy
- Remove patients from SABRIL therapy if the patients do not experience meaningful reduction in seizures
- Counsel patients who fail to comply with the program requirements
- Remove patients from SABRIL therapy who fail to comply with the program requirements after appropriate counseling

5.3 Magnetic Resonance Imaging (MRI) Abnormalities

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for Infantile Spasms (IS) with vigabatrin. In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 21.5% in vigabatrin-treated patients versus 4.1% in patients treated with other therapies.

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment. In a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied.

Neurotoxicity (including convulsions and hypomyelination) was observed in rats exposed to vigabatrin during late gestation and the neonatal and juvenile periods of development. The relationship between these findings and the abnormal MRI findings in infants treated for IS with vigabatrin is unknown [see WARNINGS AND PRECAUTIONS, Neurotoxicity (5.4) and USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)].

The specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with vigabatrin for CPS. In a blinded review of MRI images obtained in prospective clinical trials in patients with CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo patients.

For adults treated with SABRIL, routine MRI surveillance is unnecessary as there is no evidence that vigabatrin causes MRI changes in this population.

5.4 Neurotoxicity

Vacuolization, characterized by fluid accumulation and separation of the outer layers of myelin, has been observed in brain white matter tracts in adult and juvenile rats and adult mice, dogs, and possibly monkeys following administration of vigabatrin. This lesion, referred to as intramyelinic edema (IME), was seen in animals at doses within the human therapeutic range. A no-effect dose was not established in rodents or dogs. In the rat and dog, vacuolization was reversible following discontinuation of vigabatrin treatment, but, in the rat, pathologic changes consisting of swollen or degenerating axons, mineralization, and gliosis were seen in brain areas in which vacuolation had been previously observed. Vacuolization in adult animals was correlated with alterations in MRI and changes in visual and somatosensory evoked potentials (EP).

Administration of vigabatrin to rats during the neonatal and juvenile periods of development produced vacuolar changes in the gray matter (areas including the thalamus, midbrain, deep cerebellar nuclei, substantia nigra, hippocampus, and forebrain) which are considered distinct from the IME observed in vigabatrin treated adult animals. Decreased myelination, retinal dysplasia, and neurobehavioral abnormalities (convulsions, neuromotor impairment, learning deficits) were also observed following vigabatrin treatment of young rats. These effects occurred at doses associated with plasma vigabatrin levels substantially lower than those achieved clinically in infants and children.

In a published study, vigabatrin (200, 400 mg/kg/day) induced apoptotic neurodegeneration in the brain of young rats when administered by intraperitoneal injection on postnatal days 5-7.

Administration of vigabatrin to female rats during pregnancy and lactation at doses below those used clinically resulted in hippocampal vacuolation and convulsions in the mature offspring.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult

epilepsy patients have demonstrated no clear-cut abnormalities [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3)].

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including SABRIL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing SABRIL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, SABRIL should be withdrawn gradually. In controlled clinical studies in adults with CPS, SABRIL was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued [see DOSAGE AND ADMINISTRATION, General Dosing Considerations (2.3), PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.4)].

5.7 Anemia

In North American controlled trials, 5.7% of patients (16/280) receiving SABRIL and 1.6% of patients (3/188) receiving placebo had adverse events of anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled trials, there were mean decreases in hemoglobin of about 3% and 0% in SABRIL and placebo-treated patients, respectively, and in hematocrit of about 1% in Sabril treated patients compared to a gain of about 1% in patients treated with placebo.

In controlled and open label epilepsy trials, 3 SABRIL patients (0.06%, 3/4855) discontinued for anemia and 2 SABRIL patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or hematocrit below 24%.

5.8 Somnolence and Fatigue

SABRIL causes somnolence and fatigue. Patients should be advised not to drive a car or operate other complex machinery until they are familiar with the effects of SABRIL on their ability to perform such activities.

Pooled data from two SABRIL controlled trials demonstrated that 24% (54/222) of SABRIL patients experienced somnolence compared to 10% (14/135) of placebo patients. In those same studies, 28% of SABRIL patients experienced fatigue compared to 15% (20/135) of placebo patients. Almost 1% of SABRIL

patients discontinued from clinical trials for somnolence and almost 1% discontinued for fatigue.

5.9 Peripheral Neuropathy

SABRIL causes symptoms of peripheral neuropathy. In a pool of North American controlled and uncontrolled epilepsy studies, 4.2% (19/457) of SABRIL patients developed signs and/or symptoms of peripheral neuropathy. In the subset of North American placebo-controlled epilepsy trials, 1.4% (4/280) of SABRIL treated patients and no (0/188) placebo patients developed signs and/or symptoms of peripheral neuropathy. Initial manifestations of peripheral neuropathy in these trials included, in some combination, symptoms of numbness or tingling in the toes or feet, signs of reduced distal lower limb vibration or position sensation, or progressive loss of reflexes, starting at the ankles. Clinical studies in the development program were not designed to investigate peripheral neuropathy systematically and did not include nerve conduction studies, quantitative sensory testing, or skin or nerve biopsy. There is insufficient evidence to determine if development of theses signs and symptoms were related to duration of SABRIL treatment, cumulative dose, or if the findings of peripheral neuropathy were completely reversible upon discontinuation of SABRIL.

5.10 Weight Gain

SABRIL causes weight gain. Data pooled from randomized controlled trials found that 17% (77/443) of SABRIL patients versus 8% (22/275) of placebo patients gained ≥7% of baseline body weight. In these same trials, the mean weight change among SABRIL patients was 3.5 kg compared to 1.6 kg for placebo patients. In all epilepsy trials, 0.6% (31/4855) of SABRIL patients discontinued for weight gain. The long term effects of SABRIL related weight gain are not known. Weight gain was not related to the occurrence of edema.

5.11 Edema

SABRIL causes edema. Pooled data from controlled trials demonstrated increased risk among SABRIL patients compared to placebo patients for peripheral edema (SABRIL 2%, placebo 1%), and edema (SABRIL 1%, placebo 0%). In these studies, one SABRIL and no placebo patients discontinued for an edema related AE. There was no apparent association between edema and cardiovascular adverse events such as hypertension or congestive heart failure. Edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

6 ADVERSE REACTIONS

SABRIL causes permanent damage to vision in a high percentage of patients [see BOXED WARNING: VISION LOSS and WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in U.S. and Primary Non-U.S. Clinical Studies

In U.S. and primary non-U.S. clinical studies of 4,079 SABRIL treated patients, the most commonly observed (≥5%) adverse reactions associated with the use of SABRIL in combination with other AEDs were headache (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsion (11%), nasopharyngitis (10%), weight increased (10%), upper respiratory tract infection (10%), visual field defect (9%), depression (8%), tremor (7%), nystagmus (7%), nausea (7%), diarrhea (7%), memory impairment (7%), insomnia (7%), irritability (7%), coordination abnormal (7%), vision blurred (6%), diplopia (6%), vomiting (6%), influenza (6%), pyrexia (6%), and rash (6%).

The adverse reactions most commonly associated with SABRIL treatment discontinuation in ≥1% of patients were convulsion (1.4%) and depression (1.5%).

Most Common Adverse Reactions in Controlled Clinical Trials

Refractory Complex Partial Seizures in Adults

Table 2 lists the treatment emergent adverse reactions that occurred in ≥2% and more than one patient per SABRIL-treated group and that occurred more frequently than in placebo patients from 2 U.S. add-on clinical studies of refractory CPS in adults.

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Ear Disorders			
Tinnitus	3 (2)	0 (0)	2 (1)
Vertigo	3 (2)	2 (5)	2 (1)
Eye Disorders			
Vision blurred	18 (13)	7 (16)	7 (5)
Diplopia	9 (7)	7 (16)	4 (3)
Asthenopia	3 (2)	1 (2)	0 (0)
Eye pain	0 (0)	2 (5)	0 (0)
Gastrointestinal Disorders			
Diarrhoea	14 (10)	7 (16)	10 (7)
Nausea	13 (10)	1 (2)	11 (8)
Vomiting	9 (7)	4 (9)	8 (6)

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Constipation	11 (8)	2 (5)	4 (3)
Abdominal pain upper	7 (5)	2 (5)	2 (1)
Dyspepsia	6 (4)	2 (5)	4 (3)
Stomach discomfort	5 (4)	1 (2)	1 (1)
Abdominal pain	4 (3)	1 (2)	2 (1)
Toothache	3 (2)	2 (5)	3 (2)
Abdominal distension	3 (2)	0 (0)	1 (1)
General Disorders			
Fatigue	31 (23)	17 (40)	21 (16)
Gait disturbance	8 (6)	5 (12)	9 (7)
Asthenia	7 (5)	3 (7)	2 (1)
Oedema peripheral	7 (5)	3 (7)	1 (1)
Fever	6 (4)	3 (7)	4 (3)
Chest pain	2 (1)	2 (5)	2 (1)
Thirst	3 (2)	0 (0)	0 (0)
Malaise	0 (0)	2 (5)	0 (0)
Infections			
Nasopharyngitis	19 (14)	4 (9)	14 (10)
Upper respiratory tract infection	10 (7)	4 (9)	8 (6)
Influenza	7 (5)	3 (7)	5 (4)
Urinary tract infection	5 (4)	2 (5)	0 (0)
Bronchitis	0 (0)	2 (5)	2 (1)
Injury			
Contusion	4 (3)	2 (5)	3 (2)
Joint sprain	2 (1)	1 (2)	1 (1)
Muscle strain	1 (1)	1 (2)	2 (1)
Wound secretion	0 (0)	1 (2)	0 (0)
Metabolism and Nutrition Disorders			
Increased appetite	2 (1)	2 (5)	1 (1)
Weight increased	8 (6)	6 (14)	4 (3)
Musculoskeletal Disorders			
Arthralgia	14 (10)	2 (5)	4 (3)
Back pain	6 (4)	3 (7)	3 (2)
Pain in extremity	8 (6)	1 (2)	5 (4)
Myalgia	4 (3)	2 (5)	2 (1)
Muscle twitching	1 (1)	4 (9)	2 (1)
Muscle spasms	4 (3)	0 (0)	1 (1)
Nervous System Disorders			
Headache	44 (33)	11 (26)	42 (31)
Somnolence	29 (22)	11 (26)	18 (13)
Dizziness	32 (24)	11 (26)	23 (17)
Nystagmus	17 (13)	8 (19)	12 (9)
Tremor	20 (15)	7 (16)	11 (8)
Memory impairment	9 (7)	7 (16)	4 (3)

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Coordination abnormal	10 (7)	7 (16)	3 (2)
Disturbance in attention	12 (9)	0 (0)	1 (1)
Sensory disturbance	6 (4)	3 (7)	3 (2)
Hyporeflexia	6 (4)	2 (5)	1 (1)
Paraesthesia	9 (7)	1 (2)	1 (1)
Lethargy	6 (4)	3 (7)	3 (2)
Hyperreflexia	5 (4)	1 (2)	4 (3)
Hypoaesthesia	5 (4)	2 (5)	2 (1)
Sedation	5 (4)	0 (0)	0 (0)
Status epilepticus	3 (2)	2 (5)	0 (0)
Dysarthria	3 (2)	1 (2)	1 (1)
Postictal state	3 (2)	0 (0)	1 (1)
Sensory loss	0 (0)	2 (5)	0 (0)
Psychiatric Disorders			
Irritability	10 (7)	10 (23)	10 (7)
Depression	8 (6)	6 (14)	4 (3)
Confusional state	5 (4)	6 (14)	1 (1)
Anxiety	6 (4)	0 (0)	4 (3)
Depressed mood	7 (5)	0 (0)	1 (1)
Thinking abnormal	4 (3)	3 (7)	0 (0)
Abnormal behaviour	4 (3)	2 (5)	1 (1)
Expressive language disorder	2 (1)	3 (7)	1 (1)
Nervousness	3 (2)	2 (5)	3 (2)
Abnormal dreams	2 (1)	2 (5)	1 (1)
Reproductive System			
Dysmenorrhoea	12 (9)	2 (5)	4 (3)
Erectile dysfunction	0 (0)	2 (5)	0 (0)
Respiratory and Thoracic Disorders			
Pharyngolaryngeal pain	10 (7)	6 (14)	7 (5)
Cough	3 (2)	6 (14)	9 (7)
Pulmonary congestion	0 (0)	2 (5)	1 (1)
Sinus headache	8 (6)	1 (2)	1 (1)
Skin and Subcutaneous Tissue Disorders			
Rash	6 (4)	2 (5)	6 (4)

6.2 Post Marketing Experience

The following serious adverse events have been reported since approval and use of SABRIL worldwide. All serious adverse events that are not listed above as adverse events reported in clinical trials, that are not relatively common in the population and are not too vague to be useful are listed in this section. These reactions are reported voluntarily from a population of uncertain size; therefore, it

is not possible to estimate their frequency or establish a causal relationship to drug exposure. Events are categorized by system organ class.

Birth Defects: Congenital cardiac defects, congenital external ear anomaly, congenital hemangioma, congenital hydronephrosis, congenital male genital malformation, congenital oral malformation, congenital vesicoureteric reflux, dentofacial anomaly, dysmorphism, fetal anticonvulsant syndrome, hamartomas, hip dysplasia, limb malformation, limb reduction defect, low set ears, renal aplasia, retinitis pigmentosa, supernumerary nipple, talipes

Ear: Deafness

Endocrine: Delayed puberty

Gastrointestinal: Gastrointestinal hemorrhage, esophagitis

General: Developmental delay, facial edema, malignant hyperthermia, multi-organ failure

Hepatobiliary: Cholestasis

Nervous System: Dystonia, encephalopathy, hypertonia, hypotonia, muscle spasticity, myoclonus, optic neuritis

Psychiatric: Acute psychosis, apathy, delirium, hypomania, neonatal agitation, psychotic disorder

Respiratory: Laryngeal edema, pulmonary embolism, respiratory failure, stridor

Skin and Subcutaneous Tissue: Angioedema, maculo-papular rash, pruritus

7 DRUG INTERACTIONS

For detailed information about Drug Interactions see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions (12.3).

7.1 Phenytoin

A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies.

7.2 Other AEDs

There are no clinically significant pharmacokinetic interactions between SABRIL and either phenobarbital or sodium valproate. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

7.3 Clonazepam
In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

7.4 Oral Contraceptives
SABRIL is unlikely to affect the efficacy of steroid oral contraceptives.

7.5 Drug-Laboratory Test Interactions
SABRIL decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. In some patients, these enzymes become undetectable. The suppression of ALT and AST activity by SABRIL may preclude the use of these markers, especially ALT, to detect early hepatic injury.

SABRIL may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C. Vigabatrin produced developmental toxicity, including teratogenic and neurohistopathological effects, when administered to pregnant animals at clinically relevant doses. In addition, developmental neurotoxicity was observed in rats treated with vigabatrin during a period of postnatal development corresponding to the third trimester of human pregnancy. There are no adequate and well-controlled studies in pregnant women. SABRIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of vigabatrin (oral doses of 50 to 200 mg/kg) to pregnant rabbits throughout the period of organogenesis was associated with an increased incidence of malformations (cleft palate) and embryo-fetal death; these findings were observed in two separate studies. The no-effect dose for teratogenicity and embryolethality in rabbits (100 mg/kg) is approximately 1/2 the maximum recommended human dose (MRHD) of 3 g/day on a body surface area (mg/m^2) basis. In rats, oral administration of vigabatrin (50, 100, or 150 mg/kg) throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal anatomic variations. The no-effect dose for embryo-fetal toxicity in rats (50 mg/kg) is approximately 1/5 the MRHD on a mg/m^2 basis. Oral administration of vigabatrin (50, 100, 150 mg/kg) to rats from the latter part of pregnancy through weaning produced long-term neurohistopathological (hippocampal vacuolation) and neurobehavioral (convulsions) abnormalities in the offspring. A no-effect dose for developmental neurotoxicity in rats was not established; the low-effect dose (50 mg/kg) is approximately 1/5 the MRHD on a mg/m^2 basis.

In a published study, vigabatrin (300 or 450 mg/kg) was administered by intraperitoneal injection to a mutant mouse strain on a single day during organogenesis (day 7, 8, 9, 10, 11, or 12). An increase in malformations (including cleft palate) was observed at both doses.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 those measured in pediatric patients receiving an oral dose of 50 mg/kg.

Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to SABRIL, physicians are advised to recommend that pregnant patients taking SABRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http:/www.aedpregnancyregistry.org.

8.2 Nursing Mothers

Vigabatrin is excreted in human milk. Because of the potential for serious adverse reactions from vigabatrin in nursing infants [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

The safety and efficacy of SABRIL in pediatric patients (<16 years of age) with CPS has not been established.

Abnormal MRI signal changes were observed in infants [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)].

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 those measured in pediatric patients receiving an oral dose of 50 mg/kg.

8.4 Geriatric Use

Clinical studies of vigabatrin did not include sufficient numbers of patients aged 65 and over to determine whether they responded differently from younger patients.

Vigabatrin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Oral administration of a single dose of 1.5 g of vigabatrin to elderly (>65 years) patients with reduced creatinine clearance (<50 mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days. The renal clearance of vigabatrin was 36% lower in healthy elderly subjects (>65 years) than in young healthy males. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.5 Renal Impairment

Dose adjustment, including initiating treatment with a lower dose, is necessary in patients with mild (creatinine clearance >50-80 mL/min), moderate (creatinine clearance >30-50 mL/min) and severe (creatinine clearance >10-30 mL/min) renal impairment [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Class

Vigabatrin is not a controlled substance.

9.2 Abuse

Vigabatrin did not produce adverse events or overt behaviors associated with abuse when administered to humans or animals. It is not possible to predict the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking behavior).

9.3 Dependence

Following chronic administration of vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, vigabatrin should be withdrawn gradually to minimize increased seizure frequency [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6) and PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.4)].

10 OVERDOSAGE

10.1 Signs, Symptoms, and Laboratory Findings of Overdosage

Confirmed and/or suspected vigabatrin overdoses have been reported during clinical trials and in post marketing surveillance. No vigabatrin overdoses resulted in death. When reported, the vigabatrin dose ingested ranged from 3 g to 90 g, but most were between 7.5 g and 30 g. Nearly half the cases involved multiple drug ingestions including carbamazepine, barbiturates, benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine.

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of vigabatrin overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, headache, hypotension, abnormal behavior, increased seizure activity, status epilepticus, and speech disorder. These symptoms resolved with supportive care.

10.2 Treatment or Management for Overdosage

There is no specific antidote for SABRIL overdose. Standard measures to remove unabsorbed drug should be used, including elimination by emesis or gastric lavage. Supportive measures should be employed, including monitoring of vital signs and observation of the clinical status of the patients.

In an *in vitro* study, activated charcoal did not significantly adsorb vigabatrin.

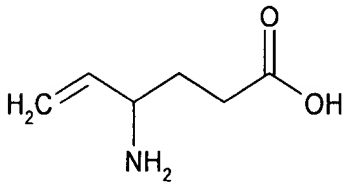
The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

11 DESCRIPTION

Table 3. Description

Proprietary Name:	SABRIL®
Established Name:	Vigabatrin Tablet
Dosage Form:	White, film-coated tablet

Table 3. Description

Route of Administration:	Oral
Pharmacologic Class of Drug:	Antiepileptic
Chemical Name:	(±) 4-amino-5-hexenoic acid
Structural Formula:	

SABRIL (vigabatrin) is available as a white, film-coated tablet for oral administration. Each tablet contains 500 mg vigabatrin. Tablets also contain as inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide. Vigabatrin is an oral antiepileptic drug with the chemical name (±) 4-amino-5-hexenoic acid. It is a racemate consisting of two enantiomers. The molecular formula is $C_6H_{11}NO_2$ and the molecular weight is 129.16.

Vigabatrin is a white to off-white powder which is freely soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n-octanol/water partition coefficient of vigabatrin is about 0.011 (log *P*=-1.96) at physiologic pH. Vigabatrin melts with decomposition in a 3-degree range within the temperature interval of 171°C to 176°C. The dissociation constants (pK_a) of vigabatrin are 4 and 9.7 at room temperature (25°C).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the central nervous system.

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

12.2 Pharmacodynamics

Effects on Electrocardiogram
There is no indication of a QT/QTc prolonging effect of SABRIL in single doses up to 6.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy subjects were administered a single oral dose of SABRIL (3 g and 6 g) and placebo. Peak concentrations for 6.0 g SABRIL were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

12.3 Pharmacokinetics

Vigabatrin displayed linear pharmacokinetics after administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g and 2.0 g twice daily with a half-life of about 7.5 hours. Bioequivalence has been established between the oral solution and tablet formulations.

Absorption
Following oral administration, vigabatrin is essentially completely absorbed. Time to maximum concentration (t_{max}) is approximately 1 hour following single and multiple doses. There was little accumulation with multiple dosing. A food effect study involving administration of vigabatrin to healthy volunteers under fasting and fed conditions indicated that the C_{max} was decreased by 33%, t_{max} was increased to 2 hours, and AUC was unchanged under fed conditions [see DOSAGE AND ADMINISTRATION (2)].

Distribution
Vigabatrin does not bind to plasma proteins. Vigabatrin is widely distributed throughout the body; mean steady-state volume of distribution is 1.1 L/Kg (CV = 20%).

Metabolism and Elimination
Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. The half-life of vigabatrin is about 7.5 hours. Following administration of $^{[14]}$C-vigabatrin to healthy male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

Pharmacokinetics in Special Populations

Geriatric
The renal clearance of vigabatrin in healthy elderly patients (≥65 years of age) was 36% less than those in healthy younger patients. This finding is confirmed by an analysis of data from a controlled clinical trial.

Gender
No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.

Race
No specific study was conducted to investigate the effects of race on SABRIL pharmacokinetics. A cross study comparison between 23 Caucasian and 7 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that the AUC, $C_{max,}$ and half-life were similar for the two populations. However, the mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4 .0 L/hr). Inter-subject variability in renal clearance was 20% in Caucasians and was 30% in Japanese.

Renal Impairment
Mean AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in patients with mild renal impairment (CLcr from >50-80 mL/min) in comparison to normal subjects.

Mean AUC increased by two-fold and the terminal half-life increased by two-fold in patients with moderate renal impairment (CLcr from >30-50 mL/min) in comparison to normal subjects.

Mean AUC increased by 4.5-fold and the terminal half-life increased by 3.5-fold in patients with severe renal impairment (CLcr from >10-30 mL/min) in comparison to normal subjects.

Dosage adjustment, including starting at a lower dose, is recommended for patients with any degree of renal impairment [see USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Hepatic Impairment
Vigabatrin is not significantly metabolized. The pharmacokinetics of vigabatrin in patients with impaired liver function have not been studied.

Drug Interactions

Phenytoin
A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies. *In vitro* drug metabolism studies indicate that decreased phenytoin concentrations upon addition of vigabatrin therapy are likely to be the result of induction of cytochrome P450 2C enzymes in some patients. Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated.

Other AEDs
When co-administered with vigabatrin, phenobarbital concentration (from phenobarbital or primidone) was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be clinically relevant. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

Clonazepam
In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

Alcohol
Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g twice daily) indicated that neither drug influences the pharmacokinetics of the other.

Oral Contraceptives
In a double-blind, placebo-controlled study using a combination oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel, vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. Based on this study, vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives. Additionally, no significant difference in pharmacokinetic parameters (elimination half-life, AUC, C_{max}, apparent oral clearance, time to peak, and apparent volume of distribution) of vigabatrin were found after treatment with ethinyl estradiol and levonorgestrel.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Vigabatrin showed no carcinogenic potential in mouse or rat when given in the diet at doses up to 150 mg/kg/day for 18 months (mouse) or at doses up to 150 mg/kg/day for 2 years (rat). These doses are less than the maximum recommended human dose (MRHD) of 3 g/day on a mg/m^2 basis.

Vigabatrin was negative in *in vitro* (Ames, CHO/HGPRT mammalian cell forward gene mutation, chromosomal aberration in rat lymphocytes) and in *in vivo* (mouse bone marrow micronucleus) assays.

No adverse effects on male or female fertility were observed in rats at oral doses up to 150 mg/kg/day (approximately 1/2 the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Complex Partial Seizures in Adults

The effectiveness of SABRIL as adjunctive therapy in adult patients with CPS was established in two U.S. multicenter, double-blind, placebo-controlled, parallel-group clinical studies. A total of 357 adults (age 18 to 60 years) with CPS, with or without secondary generalization were enrolled (Studies 1 and 2). Patients were required to be on an adequate and stable dose of an anticonvulsant, and have a history of failure on an adequate regimen of carbamazepine or phenytoin. Patients had a history of about 8 seizures per month (median) for about 20 years (median) prior to entrance into the study. These studies were not capable by design of demonstrating direct superiority of SABRIL over any other anticonvulsant added to a regimen to which the patient had not adequately responded. Further, in these studies patients had previously been treated with a limited range of anticonvulsants.

The primary measure of efficacy was the patient's reduction in mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized at end of study compared to baseline.

Study 1

Study 1 (N=174) was a randomized, double-blind, placebo-controlled, dose-response study consisting of an 8-week baseline period followed by an 18-week treatment period. Patients were randomized to receive placebo or 1, 3, or 6 g/day vigabatrin administered twice daily. During the first 6 weeks following randomization, the dose was titrated upward beginning with 1 g/day and increasing by 0.5 g/day on days 1 and 5 of each subsequent week in the 3 g/day and 6 g/day groups, until the assigned dose was reached.

Results for the primary measure of effectiveness, reduction in mean monthly frequency of Complex Partial Seizures, are shown in Table 4. The 3 g/day and 6 g/day dose groups were statistically significantly superior to placebo, but the 6 g/day dose was not superior to the 3 g/day dose.

Table 4. Median Monthly Frequency of Complex Partial Seizures+

	N	Baseline	Endstudy
Placebo	45	9.0	8.8
1 g/day SABRIL	45	8.5	7.7
3 g/day SABRIL	41	8.5	3.7*
6 g/day SABRIL	43	8.5	4.5*

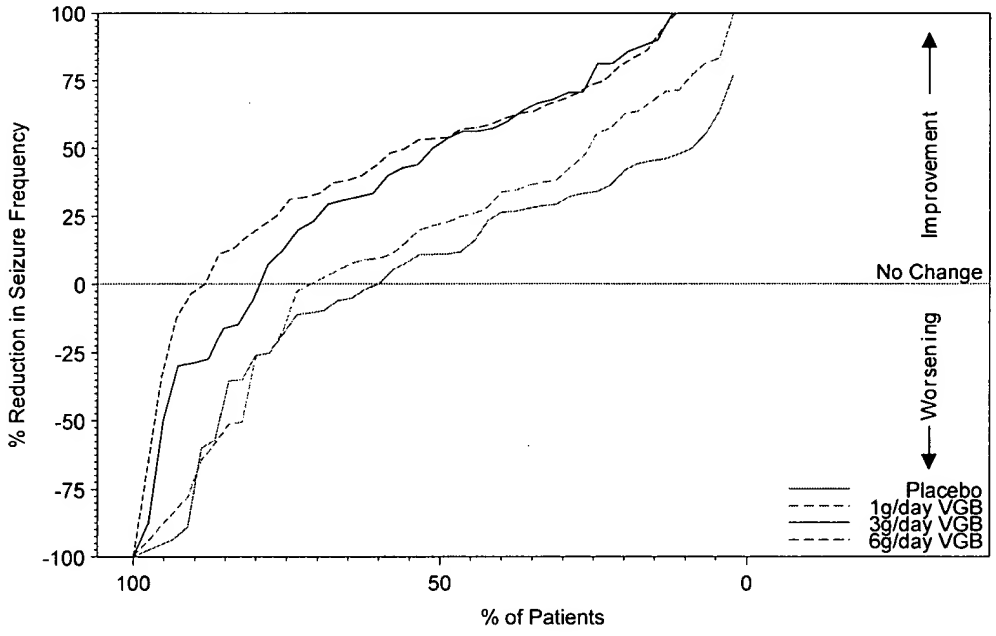
*P<0.05 compared to placebo

+Including one patient with simple partial seizures with secondary generalization only

Figure 1 presents the percentage of patients (X-axis) with a percent reduction in seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis

indicates an improvement from baseline (i.e., a decrease in complex partial seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in complex partial seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in complex partial seizure frequency was consistently higher for the SABRIL 3 and 6 g/day groups compared to the placebo group. For example, 51% of patients randomized to SABRIL3 g/day and 53% of patients randomized to Sabril 6 g/day experienced a 50% or greater reduction in seizure frequency, compared to 9% of patients randomized to placebo. Patients with an increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

Figure 1. Percent Reduction from Baseline in Seizure Frequency



Study 2

Study 2 (N=183 randomized, 182 evaluated for efficacy) was a randomized, double-blind, placebo-controlled, parallel study consisting of an 8-week baseline period and a 16-week treatment period. During the first 4 weeks following randomization, the dose of vigabatrin was titrated upward beginning with 1 g/day and increased by 0.5 g/day on a weekly basis to the maintenance dose of 3 g/day.

Table 5. Median Monthly Frequency of Complex Partial Seizures

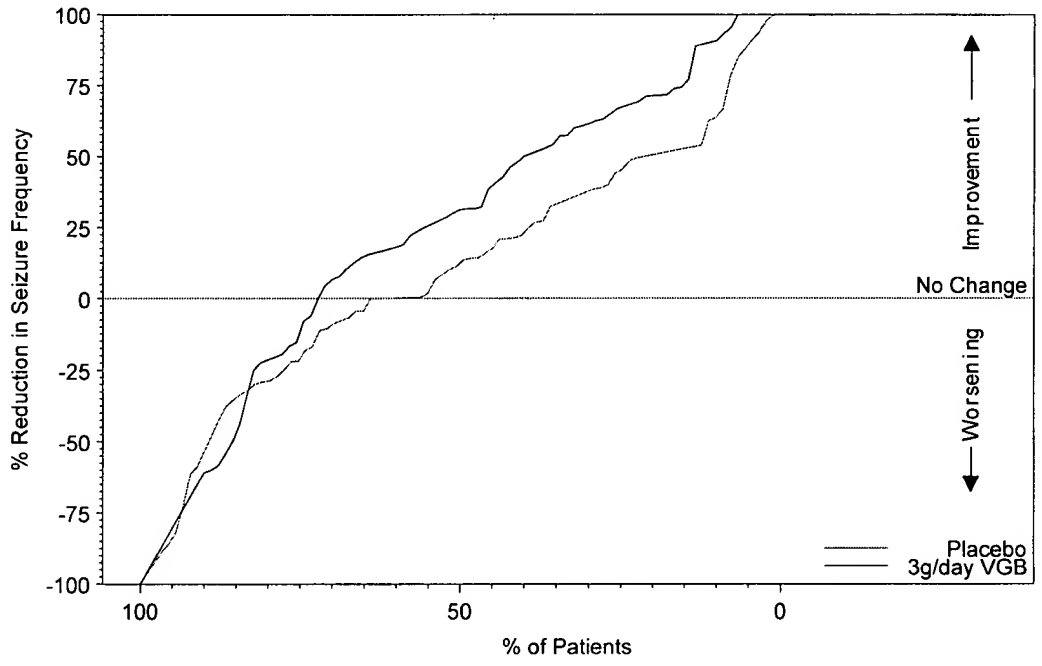
	N	Baseline	Endstudy
Placebo	90	9.0	7.5
3 g/day SABRIL	92	8.3	5.5*

*P<0.05 compared to placebo

Results for the primary measure of effectiveness, reduction in mean monthly complex partial seizure frequency, are shown in Table 5. Vigabatrin 3 g/day was statistically significantly superior to placebo in reducing seizure frequency.

Figure 2 presents the percentage of patients (X-axis) with a percent reduction in seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in complex partial seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in complex partial seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure frequency was consistently higher for the SABRIL 3 g/day group compared to the placebo group. For example, 39% of patients randomized to SABRIL (3 g/day) experienced a 50% or greater reduction in complex partial seizure frequency, compared to 21% of patients randomized to placebo. Patients with an increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

Figure 2. Percent Reduction from Baseline in Seizure Frequency



For both studies, there was no difference in the effectiveness of vigabatrin between male and female patients. Analyses of age and race were not possible as nearly all patients were between the ages of 18 to 65 and Caucasian.

15 REFERENCES

None

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 SABRIL Tablet

Each SABRIL film-coated tablet contains 500 mg vigabatrin and is white, film-coated, oval, biconvex, scored on one side, and debossed with OV 111 on the other.

NDC 67386-111-01: Bottles of 100.

Store at 20-25°C (68-77°F). See USP controlled room temperature.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.5)

Patients must be informed of the availability of a Medication Guide. Patients must be instructed to read the Medication Guide prior to initiating treatment with SABRIL and with each prescription refill. Doctors must review the SABRIL Medication Guide with every patient prior to initiation of treatment. Patients should be instructed to take SABRIL only as prescribed.

17.1 Vision Loss

Patients should be informed of the risk of permanent vision loss, particularly loss of peripheral vision, from SABRIL, and the need for monitoring vision [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

Monitoring of vision, including assessment of visual fields and visual acuity, is required for adults at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy unless after repeated attempts it is not possible. In those patients in whom vision testing is not possible, treatment may continue according to clinical judgment with appropriate patient counseling and with documentation in the SHARE program of the inability to test vision. Patients should be informed that if baseline or subsequent vision is not normal, SABRIL should only be used if the benefits of SABRIL treatment clearly outweigh the risks of additional vision loss.

Patients should understand that vision testing may be insensitive and may not detect vision loss before it is severe. Patients should also understand that if vision loss is documented, such loss is irreversible.

Patients should be informed that if changes in vision are suspected, they should notify their physician immediately.

17.2 Suicidal Thinking and Behavior

Patients, their caregiver(s), and families should be counseled that AEDs, including SABRIL, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of concern should be reported immediately to healthcare providers [see WARNINGS AND PRECAUTIONS, Suicidal Behavior and Ideation (5.5)].

17.3 Use in Pregnancy

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1), and Nursing Mothers (8.2)].

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)]. Information on the registry can also be found at the website http:/www.aedpregnancyregistry.org.

17.4 Withdrawal of SABRIL Therapy

Patients should be told not to suddenly discontinue SABRIL therapy. As with all AEDs, withdrawal should be gradual. In controlled clinical studies in adults with CPS, vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued.

17.5 FDA-Approved Medication Guide

MEDICATION GUIDE

SABRIL® (*SAY-bril*)
(vigabatrin) Tablet

SABRIL® (*SAY-bril*)
(vigabatrin) for Oral Solution

Read the Medication Guide that comes with SABRIL before you or your baby starts taking SABRIL and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your or your baby's medical condition or treatment.

What is the most important information I should know about SABRIL?

SABRIL can cause serious side effects, including:

- **Permanent vision damage:**
  SABRIL can damage the vision of anyone who takes it. The most noticeable loss is in your ability to see to the side when you look straight ahead (peripheral vision). If this happens, it will not get better. People who take SABRIL do not lose all of their vision, but some people can have severe loss particularly to their peripheral vision. With severe vision loss you may only be able to see things straight in front of you (sometimes called 'tunnel vision'). You may also have blurry vision.

- **Vision loss and use of SABRIL in adults:** Because of the risk of vision loss, SABRIL is used to treat complex partial seizures (CPS) only in people who do not respond well enough to several other medicines.

Tell your doctor right away if you:

- think you are not seeing as well as before you started taking SABRIL
- start to trip, bump into things, or are more clumsy than usual
- are surprised by people or things coming in front of you that seem to come out of nowhere

These changes can mean that you have damage to your vision. Your doctor will test your visual fields (including peripheral vision) and visual acuity (ability to read an eye chart) before you start SABRIL or within 4 weeks after starting SABRIL, and at least every 3 months after that until SABRIL is stopped. Even if your vision seems fine, it is important that you get these regular vision tests because damage can happen to your vision before you notice any changes. These vision tests cannot prevent the vision damage that can happen with SABRIL, but they do allow you to stop SABRIL if vision has gotten worse, which usually will lessen further damage. If you do not have these vision tests regularly, your doctor may stop prescribing SABRIL for you. You should also have a vision test after SABRIL is stopped.

If you drive and your vision is damaged by SABRIL, driving might be more dangerous, or you may not be able to drive safely at all. You should discuss this with your doctor.

- **Vision loss in babies:** Because of the risk of vision loss, SABRIL is used in babies (1 month to 2 years old) with infantile spasms (IS) only when you and your doctor decide that the possible benefits of SABRIL are more important than the risks. Parents or caregivers are not likely to recognize the symptoms of vision loss in babies until it is severe. Doctors may not find vision loss in babies until it is severe. It is difficult to test vision in babies, but all babies should have a vision test before starting SABRIL or within 4 weeks after starting SABRIL, and every 3 months after that until SABRIL is stopped. You should have a vision test for your baby after SABRIL is stopped.

Tell your doctor right away if you think that your baby is:

- not seeing as well as before taking SABRIL
- acting differently than normal

Even if your baby's vision seems fine, it is important to get regular vision tests because damage can happen before your baby acts differently. Even these regular vision exams may not show the damage to your baby's vision before it is serious and permanent. If your baby does not have these vision tests regularly, your doctor may stop prescribing SABRIL for your baby. If your baby is not able to complete vision testing, your doctor may continue prescribing SABRIL for your baby. But, your doctor will not be able to watch for vision loss in your baby.

In all people who take SABRIL:

- You are at risk for vision loss with any amount of SABRIL
- Your risk of vision loss may be higher the more SABRIL you take daily and the longer you take it
- It is not possible for your doctor to know when vision loss will happen. It could happen soon after starting SABRIL or any time during treatment. It may even happen after treatment has stopped.

Because Sabril might cause vision loss, it is available to doctors and patients only under a special program called SHARE. As part of the SHARE program, among other things, your doctor will have to test your or your baby's vision frequently while you or your baby are being treated with Sabril, and even after you or your baby stops treatment. You also have to agree to be in the SHARE program, and agree to have your or your baby's vision tested regularly. Your doctor will explain the details of the SHARE program to you.

MRI changes. Brain pictures taken by magnetic resonance imaging (MRI) show changes in some babies after they are given SABRIL. It is not known if these changes are harmful.

Risk of suicidal thoughts or actions. Like other antiepileptic drugs, SABRIL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it. Call a doctor right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your doctor as scheduled.
- Call your doctor between visits as needed, especially if you are worried about symptoms.

Do not stop SABRIL without first talking to a healthcare provider.

- Stopping SABRIL suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures.

SABRIL can be prescribed only to people who are enrolled in a program called SHARE. Before you or your baby can begin taking SABRIL, you must read and agree to all of the instructions in the SHARE program.

What is SABRIL?

SABRIL Tablets is a prescription medicine used along with other treatments to treat adults with CPS if:

- The CPS does not respond well enough to several other treatments, and
- You and your doctor decide the possible benefit of taking SABRIL is more important than the risk of vision loss.

SABRIL should not be the first medicine used to treat your CPS.

SABRIL for Oral Solution is a prescription medicine used to treat babies, one month to two years old who have IS, if you and your doctor decide the possible benefits of taking SABRIL are more important than the possible risk of vision loss.

If you are an adult with CPS, you must sign an agreement form before you can receive SABRIL.

If you are the parent or caregiver of a baby with IS, you must sign an agreement form before your baby can receive SABRIL.

What should I tell my doctor before starting SABRIL?

If you are an adult with CPS, before taking SABRIL tell your doctor if you have or had:

- depression, mood problems or suicidal thoughts or behavior
- an allergic reaction to SABRIL, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems
- low red blood cell counts (anemia)
- any nervous or mental illnesses, such as depression, thoughts of suicide, or attempts at suicide
- any other medical conditions
- are breastfeeding or planning to breastfeed. SABRIL can pass into breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take SABRIL.
- are pregnant or plan to become pregnant. It is not known if SABRIL will harm your unborn baby. You and your healthcare provider will have to decide if you should take SABRIL while you are pregnant.

Pregnancy Registry:

If you become pregnant while taking SABRIL, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy.

Before giving SABRIL to your baby, tell the doctor about all of your baby's medical conditions, including if your baby has or ever had:

- an allergic reaction to SABRIL, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems

Tell your doctor about all the medicines you or your baby take, including prescription and non-prescription medicines, vitamins, and herbal supplements. SABRIL and other medicines may affect each other causing side effects.

How should I take SABRIL?

If you are an adult with CPS:

- Your doctor will explain the SHARE Program to you
- You will receive SABRIL from a specialty pharmacy
- Take SABRIL tablets exactly as prescribed by your doctor. SABRIL tablets are usually taken two times each day.
- You may take SABRIL tablets with or without food
- Before you start taking SABRIL, talk to your doctor about what you should do if you miss a dose of SABRIL
- **Do not stop taking SABRIL suddenly.** This can cause serious problems. Stopping SABRIL or any seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures. You should follow your doctor's instructions on how to stop taking SABRIL.
- Tell your doctor right away about any increase in seizures while you are stopping SABRIL
- If SABRIL does not improve your seizures enough within 3 months, your doctor will stop prescribing SABRIL for you
- **Do not stop taking SABRIL without talking to your doctor.** If SABRIL improves your seizures, you and your doctor should talk about whether the benefit of taking SABRIL is more important than the risk of vision loss, and decide if you will continue to take SABRIL.

If you are giving SABRIL to your baby for IS:

- Your doctor will explain the SHARE program to you
- You will receive SABRIL for oral solution from a specialty pharmacy
- Mix SABRIL for oral solution and give it to your baby exactly as prescribed by your doctor. Do not stop giving SABRIL for oral solution to your baby unless your doctor tells you to.
- SABRIL for oral solution is usually given two times each day

- SABRIL for oral solution can be given to your baby at the same time as their food, but the powder should not be mixed with their food. SABRIL for oral solution powder should be mixed with water only.
- See the end of this Medication Guide for detailed instructions for how to mix SABRIL for oral solution and give the medicine to your baby
- Before your baby starts taking SABRIL, speak to your baby's doctor about what to do if your baby misses a dose, vomits, spits up, or only takes part of the dose of SABRIL
- **Stopping SABRIL suddenly can cause serious problems**. Stopping SABRIL or any seizure medicine suddenly can cause seizures that will not stop. You should follow your doctor's instructions on how to stop giving SABRIL to your baby. SABRIL does not work in all babies. If your baby's seizures do not improve enough within 2 to 4 weeks, the doctor will stop SABRIL.
- **Tell your doctor right away about any increase in your baby's seizures while stopping SABRIL**

What should I avoid while taking SABRIL?

SABRIL causes sleepiness and tiredness. Adults taking SABRIL should not drive, operate machinery, or perform any hazardous task, unless you and your doctor have decided that you can do these things safely.

What are the possible side effects of SABRIL?

SABRIL can cause serious side effects. See "What is the most important information I should know about SABRIL?"

These other serious side effects happen in **adults**. It is not known if these side effects also happen in babies who take SABRIL.

- Low red blood cell counts (anemia)
- Sleepiness and tiredness. See "What should I avoid while taking SABRIL?"
- Nerve problems. Symptoms of a nerve problem can include numbness and tingling in your toes or feet. It is not known if nerve problems will go away after you stop taking SABRIL.
- Weight gain that happens without swelling
- Swelling

If you are an adult with CPS, SABRIL may make certain types of seizures worse. Tell your doctor right away if your seizures get worse.

The most common side effects of SABRIL in adults include:

- problems walking or feel uncoordinated
- feel dizzy
- shaking (tremor)
- joint pain
- memory problems and not thinking clearly
- eye problems: blurry vision, double vision and eye movements that you cannot control

If you are giving SABRIL to your baby for IS

SABRIL may make certain types of seizures worse. You should tell your baby's doctor right away if your baby's seizures get worse. Tell your baby's doctor if you see any changes in your baby's behavior.

The most common side effects of SABRIL in **babies and young children** include:

- sleepiness - SABRIL may cause your baby to be sleepy. Sleepy babies may have a harder time suckling and feeding, or may be irritable.
- ear infection
- irritability

Tell your doctor if you or your baby have any side effect that bother you or that does not go away. These are not all the possible side effects of SABRIL. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SABRIL?

Store SABRIL tablets and SABRIL packets at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep SABRIL tablets and SABRIL powder in the container they come in.

Keep SABRIL and all medicines out of the reach of children.

General information about SABRIL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SABRIL for a condition for which it was not prescribed. Do not give SABRIL to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SABRIL. If you would like more information about SABRIL, talk with your doctor. You can ask your pharmacist or doctor for information about SABRIL that is written for health professionals. For more information, go to **www.SABRIL.net or call 1-800-455-1141.**

What are the ingredients in SABRIL?

Active Ingredient: vigabatrin

Inactive Ingredients in **SABRIL tablets**: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide.

Inactive Ingredient in **SABRIL powder**: povidone.

Instructions for mixing and giving SABRIL for oral solution to your baby

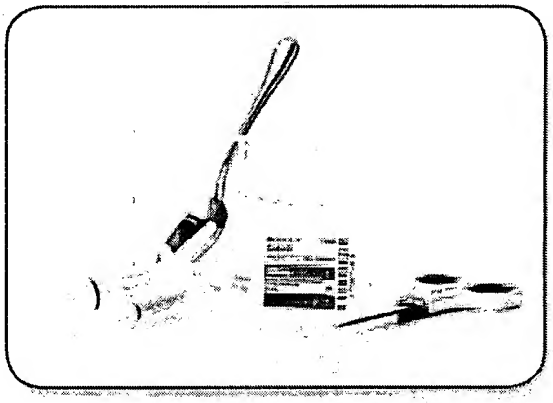
Sabril®
vigabatrin
500 mg tablet
500 mg powder for oral solution

Be sure to read, understand, and follow these instructions for the right way to mix SABRIL for oral solution to give to your baby. Talk to your doctor if you have any questions about the right dose of medicine to give your baby or how to mix it.

- SABRIL for oral solution comes as a powder
- Each packet contains 500 mg of SABRIL for oral solution
- The powder in the packets must be mixed with **water only.** The water may be cold or at room temperature
- Your baby's doctor will tell you:
  - how many packets of SABRIL for oral solution your baby will need for each dose
  - how many milliliters (mLs) of water to use to mix a dose of SABRIL for oral solution for your baby
  - how many milliliters (mLs) of the mixture you will need to give to your baby after the powder is mixed with water. This is the amount of medicine to give your baby for one dose of SABRIL for oral solution
- SABRIL for oral solution should be given to your baby right away after it is mixed

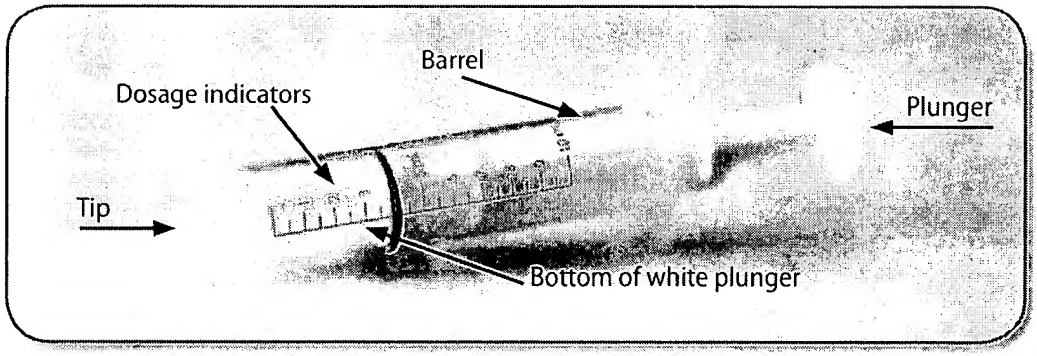
Supplies needed to mix a dose of SABRIL for oral solution:

- The number of packets of SABRIL for oral solution needed for your baby's dose
- 2 clean cups: 1 for mixing and 1 for water. The cup used for mixing SABRIL for oral solution should be clear so you can see if the powder is dissolved
- Water to mix with the SABRIL for oral solution
- Small 3 mL oral syringe and large 10 mL oral syringe provided
- Small spoon or other clean utensil to stir with
- Scissors



S·H·A·R·E®
Support, Help And Resources for Epilepsy

Oral syringe detail



1. Get **1** of the empty cups and the number of packets you will need for 1 dose.

2. Before you open the packet, tap it to settle all the powder at the bottom of the packet.

3. Use a pair of scissors to cut open the SABRIL for oral solution packet along the dotted line.

4. Empty the entire contents of the SABRIL for oral solution packet into **1** of the clean empty cups (Figure A).

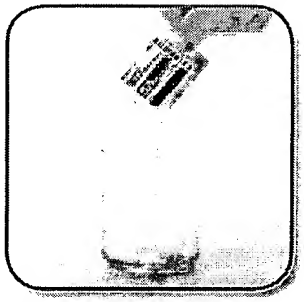


Figure A

5. Repeat steps 2 through 4 above to open all of the packets needed for 1 dose of SABRIL for oral solution.

6. Get the **other** cup and fill it half way with water (Figure B). Do not mix SABRIL for oral solution with anything other than water.

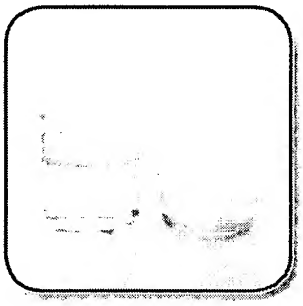


Figure B

7. You will use the larger oral syringe (10 mL) to draw up the water needed to mix with the powder from the packets. **Each packet of SABRIL for oral solution needs to be mixed with 10 mL of water.**

   For example:

   - If you are using 1 packet of SABRIL for oral solution, you will need to use 10 mL of water (fill the 10 mL oral syringe 1 time)
   - If you are using 2 packets of SABRIL for oral solution, you will need to use 20 mL of water (fill the 10 mL oral syringe 2 times)
   - If you are using 3 packets of SABRIL for oral solution, you will need to use 30 mL of water (fill the 10 mL oral syringe 3 times)

8. Get the **larger** oral syringe (the 10 mL oral syringe). Use the oral syringe to draw up 10 mL of water. To do this, put the **tip** of the oral syringe all the way into the water in your cup. Then pull the plunger up towards you until the black ring of the white plunger is at the 10 mL line on the barrel of the oral syringe (Figure C).

Figure C

9. If you see bubbles of air in the oral syringe after drawing up the water, turn the oral syringe so the tip is pointing up (Figure D). The air will move to the top of the oral syringe. Pull the plunger back towards you and then push it back gently into the oral syringe to get rid of the bubbles. Tiny bubbles are normal.

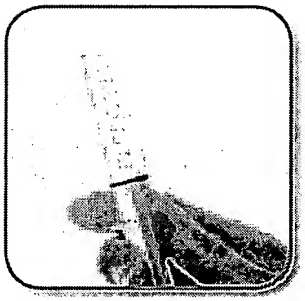


Figure D

10. Make sure the oral syringe is full of water up to the 10 mL line (Figure E).

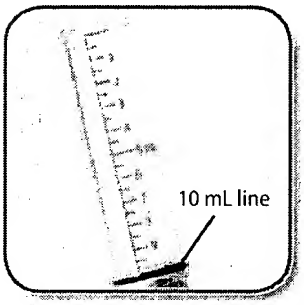


Figure E

11. Empty the water from the oral syringe directly into the cup with the SABRIL for oral solution. This is done by pushing the plunger of the oral syringe down **slowly** while the tip of the oral syringe is in the cup (Figure F).

Repeat steps 8 through 11 until all of the water that is needed to mix 1 dose of SABRIL for oral solution has been added to the cup containing the powder.

Figure F

12. Stir the mixture with the small spoon or other clean utensil until the solution is clear (Figure G). This means that all of the powder is dissolved.

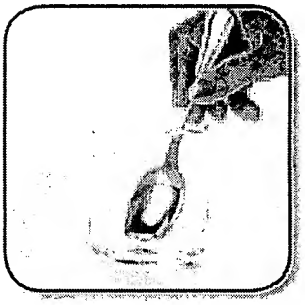


Figure G

13. Use the oral syringe to draw up the number of mLs of the mixture told to you by your doctor. If you are giving **3 mL or less** of the mixture, use the smaller oral syringe (3 mL oral syringe). If you are giving **more than 3 mL** of the mixture, use the 10 mL oral syringe. (This is the oral syringe that you just used to add the water.)

14. Put the **tip** of the oral syringe all the way into the mixture. Pull the plunger up towards you to draw up the mixture. Stop when the black ring of the white plunger lines up with the marking on the barrel of the oral syringe that matches the number of mLs of mixture your doctor told you to give your baby (Figure H).

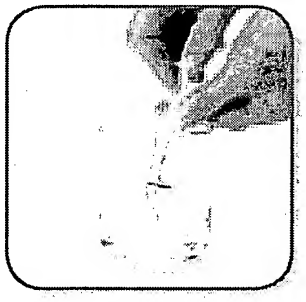


Figure H

15. If you see bubbles or air in the oral syringe after drawing up the mixture, turn the oral syringe so the tip is pointing up (Figure I). The air will move to the top of the oral syringe. Pull the plunger back towards you and then gently push it back in the oral syringe in order to get rid of the bubbles. Tiny bubbles are normal.

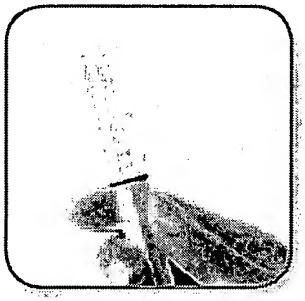


Figure I

16. Place the tip of the oral syringe into your baby's mouth and point the oral syringe towards either of the baby's cheeks (Figure J). Push on the plunger slowly, **a small amount at a time,** until all of the mixture in the oral syringe is given.

Figure J

17. If the dose you are giving your baby is larger than 10 mL, repeat steps 14 through 16 until you give the total dose of mixture prescribed by the doctor.

18. Throw away any mixture that is left over. Do not save and reuse leftover mixture.

19. Wash the oral syringes and mixing cups in warm water. To clean the oral syringes, remove the plunger by gently pulling it straight out of the barrel. The barrel and plunger can be hand washed with soap and water, rinsed, and allowed to dry, or the barrel and plunger can be placed in a dishwasher utensil rack, machine washed, and dried.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Marketed by:
Insert Lundbeck Inc. logo
Lundbeck Inc.
Deerfield, IL 60015, U.S.A.

Insert Lundbeck Inc. logo

Issued August 2009

NDC 67386-111-01 100 Tablets

Each Tablet Contains:
vigabatrin ..... **500 mg**

See package insert for full prescribing information.

Store at controlled room temperature, 20-25°C (68-77°F).

Dispense in a USP tight container.

Manufactured by: Patheon
York Mills (Ontario), Canada
For: Lundbeck Inc.
Deerfield, IL 60015, U.S.A.

® Trademark of Lundbeck Inc.

Sabril®
(vigabatrin) Tablets

500 mg

DISPENSE THE ENCLOSED MEDICATION GUIDE WITH EACH PRESCRIPTION.

℞ only

Lundbeck Inc.
Deerfield, IL 60015, U.S.A.

LOT EXP.

70019781

3 67386 11101 1

APPENDIX A

RISK EVALUATION & MITIGATION STRATEGY (REMS)

Title:	Risk Evaluation & Mitigation Strategy (REMS): Support, Help and Resources for Epilepsy (SHARE)
Product Name:	Sabril (vigabatrin) NDAs 20-427, 22-006
Sponsor:	Lundbeck Inc. Four Parkway North Deerfield, Illinois 60015 Jenny Swalec, Sr. Director, Global Regulatory Affairs 847-282-1066
Date:	21 August 2009

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

The goals of the REMS are:

1) To reduce the risk of a Sabril-induced vision loss while delivering benefit to the appropriate patient populations;

2) To ensure that all patients receive a baseline ophthalmologic evaluation; 50% of patients will receive within 2 weeks of starting Sabril and 100% within 4 weeks;

3) To discontinue Sabril therapy in patients who experience an inadequate clinical response;

4) To detect Sabril-induced vision loss as early as possible;

5) To ensure regular vision monitoring to facilitate ongoing benefit-risk assessments; and

6) To inform patients/parent or legal guardian of the serious risks associated with Sabril, including vision loss and increased risk of suicidal thoughts and behavior.

II. REMS ELEMENTS

A. Medication Guide

Lundbeck will ensure that a Medication Guide is dispensed with each prescription of Sabril and in accordance with 21CFR 208.24. The Medication Guide will be included in the Sabril Starter Kit to be reviewed with the patient/parent or legal guardian by the physician prior to starting the patient on Sabril therapy.

Please see appended Medication Guide.

B. Communication Plan

At product launch (that is, during the first 6 months after product approval) and yearly for 3 years thereafter Lundbeck will send a Dear Healthcare Professional Letter via direct mail to all registered ophthalmologists. The Sabril package insert will accompany the letter. Additionally, Lundbeck Inc. field representatives will call on neuro-ophthalmologists and/or ophthalmologists at key epilepsy centers at product launch to disseminate the Sabril package inserts.

The Dear Healthcare Professional Letter is part of the REMS and is appended.

C. Elements To Assure Safe Use

1) Healthcare providers who prescribe Sabril will be specially certified under 505-1 (f)(3)(A).
   a) Lundbeck Inc. will ensure that prescribers enrolled in the REMS program are specially certified. Lundbeck Inc. will ensure that, to become certified, prescribers attest to their understanding of the REMS program requirements and the risks associated with Sabril, and that prescribers commit to the following:
      i) Reading the full prescribing information (PI) and Medication Guide;
      ii) Having knowledge of the approved indications for Sabril;
      iii) Having experience in treating epilepsy;
      iv) Having knowledge of the risks of Sabril, especially vision loss;
      v) If prescribing for infantile spasms, having knowledge of the risk of MRI abnormalities with use of Sabril;
      vi) Assessing the effectiveness of Sabril within 2-4 weeks in infants and within 12 weeks in adults; in the case that insufficient clinical benefit has occurred, Sabril will be discontinued; for patients discontinuing Sabril at this evaluation, a Treatment Maintenance Form will not be completed; for patients continuing

treatment, a Treatment Maintenance Form will be completed and faxed to the REMS coordinating center;

vii) Ordering and reviewing visual assessment at the time of initiation of Sabril using the Ophthalmologic Assessment Form (with the baseline assessment to be conducted within 4 weeks of starting Sabril), and every 3 months after initiating Sabril therapy; the Ophthalmologic Assessment Form will be faxed to the REMS coordinating center;

viii) Educating patients on the risks and benefits of Sabril;

ix) Enrolling all patients who take Sabril in the REMS program by completing and submitting the Treatment Initiation Form and the Patient/Parent/Legal Guardian-Physician Agreement Form;

x) Reviewing the Sabril Medication Guide with every patient;

xi) Counseling the patient if the patient is not complying with the required vision monitoring beyond the baseline test, and removing the patient from therapy if the patient still fails to comply with required vision monitoring;

(1) Should discontinuation be required, discontinuation will be accomplished by tapering the patient from therapy as described in the therapy by tapering the patient from therapy as described in the Dear HCP Medication Taper Letter; and

xii) Reporting to the Sponsor at 1-800-455-1141 any serious adverse events with Sabril and providing all known details of the event.

b) The prescriber may exempt certain patients from vision assessment, using the Ophthalmologic Assessment form, if:

i) The patient is blind

ii) The patient's general neurological condition precludes the need for visual assessment

iii) The patient's medical condition prevents visual assessment being performed safely, documented by the prescriber.

iv) For other reasons documented by the prescriber.

c) The following materials are part of the REMS and are appended

(1) Dear Healthcare Professional (HCP) Letter

(2) Dear HCP Medication Taper Letter

(3) Prescriber Enrollment and Agreement Form

(4) Treatment Initiation Form

(5) Treatment Maintenance Form

(6) Ophthalmologic Assessment Form

(7) Patient-Physician Agreement- Refractory CPS

(8) Parent/Legal Guardian –Physician Agreement-IS

Lundbeck Inc. will maintain a database of certified prescribers in the REMS program. Lundbeck Inc. will ensure that prescribers comply with the requirements of the REMS and may de-enroll noncompliant prescribers.

2) Pharmacies that dispense Sabril will be specially certified by Lundbeck Inc, under 505-1(f)(3)(B).

Lundbeck Inc. will ensure that to be certified, each pharmacy does the following; pharmacies not complying may be de-enrolled by Lundbeck Inc:

a) designates a representative who is trained on the REMS program

b) dispenses Sabril only to patients who are enrolled in the REMS program, and whose continued eligibility has been established within the REMS

c) obtains treatment forms and prescriptions only from the REMS coordinating center.

d) obtains a dispensing authorization from the REMS coordinating center before dispensing the first Sabril prescription and before dispensing each refill.

e) trains pharmacy staff on the REMS program procedures and REMS materials for dispensing

f) agrees that the certified pharmacy may be audited by the FDA, Lundbeck Inc, or a third party designated by Lundbeck Inc.

3) Sabril will be dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D):

a) Lundbeck Inc. will ensure that each patient treated with Sabril is enrolled in the Sabril REMS before Sabril is dispensed to him or her. Lundbeck Inc. will ensure that, to become enrolled, each patient or parent/legal guardian must sign a Patient/Parent/Legal Guardian-Physician Agreement Form indicating that:

i) they have read the Medication Guide;

ii) the prescriber has explained the risk of visual loss;

iii) vision loss, should it occur, is irreversible;

iv) that prescribed vision assessments must be obtained;

v) periodic vision assessment, although it does not protect against all vision loss, is required for the duration of therapy, and after stopping Sabril; and

vi) response to Sabril will be assessed after a short trial period (3 months for complex partial seizures and 1 month for infantile spasms); should the patient's response to Sabril be insufficient, therapy with Sabril will be stopped

b) The following materials are part of the REMS and are appended

(1) Patient-Physician Agreement- Refractory CPS

(2) Parent/Legal Guardian –Physician Agreement-IS

(3) Treatment Maintenance Form

(4) Ophthalmologic Assessment Form

4) Each patient using the drug will be enrolled in a registry under 505-1(f)(3)(F) The registry will collect prescriber specialty, patient demographics, diagnosis, prior and concurrent anti-seizure medications, periodic ophthalmologic assessment data (i.e., the results of every 3-month monitoring), and the proportion of patients receiving Sabril for refractory complex partial seizures and infantile spasms who respond/do not respond to Sabril during the treatment initiation phase.

D. Implementation System

The Implementation System will include the following. Lundbeck Inc. will:

1) maintain a validated and secured (21 CFR Part 11 compliant) database of certified pharmacies, certified prescribers and enrolled patients.

2) monitor distribution data to ensure that only certified pharmacies are distributing and dispensing Sabril.

3) train all personnel working for the REMS coordinating center (TheraCom) directly responsible for the Sabril REMS program and site managers at all certified pharmacies. Lundbeck Inc. will audit all certified pharmacies and the REMS coordinating center on an annual basis.

4) ensure that the REMS coordinating center receives each enrolled patient's completed Treatment Maintenance Form documenting an assessment of risk-benefit prior to authorizing the maintenance phase of therapy.

5) ensure that the REMS coordinating center obtains the completed Ophthalmologic Assessment Form for all registered patients at 3-month intervals (plus a 90-day grace period, as detailed in the REMS Supporting Document) prior to authorizing continued dispensing of refills

6) ensure that certified pharmacies dispense Sabril only if they receive authorization for each dispensing from the REMS coordinating center.

7) ensure that patients who do not comply with the vision monitoring requirements of the REMS are tapered from Sabril.

8) monitor and evaluate the implementation of the elements provided for under Sections C1, C.2, C.3, and C.4, above, in the manner described in the REMS supporting document, and take reasonable steps to work to improve implementation of these elements.

E. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA every 6 months from the date of approval of the REMS for 1 year, and then annually thereafter. The assessment period will close no earlier than 60 days prior to the date the respective assessment is due. The assessment is to be received by the FDA on the due date.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

Lundbeck Inc. is writing to inform you of the approval of SABRIL® (vigabatrin), pronounced say-bril, by the Food and Drug Administration (FDA) for the following indications: As adjunctive therapy in adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments and as monotherapy for pediatric patients with infantile spasms (IS).

Decisions to use SABRIL to treat refractory CPS and IS must balance the potential benefits with the risks of therapy.

SABRIL causes irreversible bilateral concentric constriction of the visual field in 30 percent or more of adult patients, and, therefore, has a Risk Evaluation and Mitigation Strategy (REMS) associated with its use. Information on how patients and physicians can gain access to SABRIL and guidance on how to evaluate SABRIL-induced vision loss can be found through the SHARE Program which is discussed at the end of this letter.

Copies of the full Prescribing Information and Medication Guide are enclosed for your reference. Two specific effects of SABRIL are highlighted below:

Vision Loss
SABRIL causes permanent bilateral concentric constriction of the visual field in 30 percent or more of adult patients. Vision loss can range in severity from mild to severe, including tunnel vision to within about 10 degrees of visual fixation and can result in disability. In some cases, SABRIL can also damage the central retina and may decrease visual acuity. The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years, although the risk of vision loss may increase with increasing duration of exposure. There is no dose known to be free of risk of vision loss, although the risk of vision loss may increase with increasing dose and cumulative exposure. The possibility that vision loss can worsen despite discontinuation of SABRIL has not been excluded.

Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe; therefore, appropriate vision monitoring is needed for detection. Monitoring of vision by an ophthalmic professional (defined as having expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina) is required.

Vision monitoring is mandatory in adults receiving SABRIL for refractory CPS at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.

Assessing vision loss is difficult in children and therefore the frequency and extent of vision loss in infants and children is poorly characterized. Vision monitoring is required to the extent possible in infants receiving SABRIL at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. This assessment should include visual acuity and visual field whenever possible. The appropriate diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor periodically must be documented under the SHARE program. In those patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate caregiver counseling, and

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

with documentation in the SHARE program of the inability to test vision. Results from ophthalmic monitoring must be interpreted with caution, as reliability and predictive value are variable

Please read the full Prescribing Information for additional details.

Magnetic Resonance Imaging (MRI) Abnormalities

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated with SABRIL. The potential for long-term clinical sequelae and the need for monitoring have not been adequately studied. In animals that received vigabatrin, similar MRI abnormalities were correlated histologically with microvacuoles, consistent with a process of intramyelinic edema in those animals. Vacuolar changes considered distinct from intramyelinic edema, as well as other neurotoxicity and neurobehavioral abnormalities have also been observed in animals.

Brain MRI abnormalities, attributable to SABRIL have not been observed in adult or older pediatric patients treated with SABRIL for CPS.

Please read the full Prescribing Information for additional details.

S.H.A.R.E Program

To support patients and prescribers in their evaluation of the benefits and risks of SABRIL and their decision to initiate therapy, and to support the evaluators of SABRIL induced vision loss, Lundbeck Inc. has established the SHARE program which stands for Support, Help and Resources for Epilepsy. SHARE administers the SABRIL Risk Evaluation & Mitigation Strategy (REMS) program and the associated distribution and reimbursement services. All physicians who prescribe SABRIL and all patients who take SABRIL must be registered in the SHARE program. Ophthalmologists do not need to be registered.

Please visit the Lundbeck SHARE website at www.lundbeckshare.com or call SHARE at 1-888-45-SHARE for registration information. Medical inquiries should be directed to the Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Patient Safety Department at 1-800-455-1141.

Sincerely,

Lundbeck Inc.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

Based on our conversation with you on *(insert date)*, you indicated that you wish to continue treating patient, *(insert name)* with SABRIL after their completed Evaluation Phase of SABRIL therapy. We are writing to inform you that since we have not received a Treatment Maintenance Form for your patient, *(insert name)* which is mandatory for continued treatment with SABRIL, your next prescription must be written to taper *(insert name)* off of SABRIL, as no additional refills will be provided following completion of the taper.

This letter serves to remind you of the potential issues surrounding the abrupt withdrawal of SABRIL and provides the medication tapering recommendations from the Withdrawal of SABRIL Therapy Section of the approved labeling.

- SABRIL should not be discontinued abruptly and suddenly.
- As with all antiepileptic drugs, SABRIL should be withdrawn gradually to minimize increased seizure frequency.

An example of a tapering schedule employed in controlled clinical studies in adults with complex partial seizures is as follows: Vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued. For example, if a patient was taking 3 g/day, the taper schedule was:

- Week 1: 2 g/day = two tablets twice per day = 28 tablets total
- Week 2: 1 g/day = one tablet twice per day = 14 tablets total
- Week 3: Sabril completely discontinued

This example tapering schedule would require a total of 42 tablets of SABRIL.

An example of a tapering schedule employed in a controlled clinical study in patients with infantile spasms is as follows: Vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days. For example if a patient was taking 150 mg/kg/day (75 mg/kg BID), the taper schedule was:

- Days 1-3: 100 mg/kg/day (50 mg/kg BID)
- Days 4-6: 50 mg/kg/day (25 mg/kg BID)
- Days 7-10: 25 mg/kg/day (12.5 mg/kg BID)
- Day 11: Vigabatrin completely discontinued.

Read the full Prescribing Information in the approved labeling for additional details.

Please call the SHARE call center at 1-888-45-SHARE with any questions, concerns, or updates regarding this patient.

Other medical inquiries should be directed to the Lundbeck Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Lundbeck Patient Safety Department at 1-800-455-1141.

Sincerely,

Lundbeck Inc.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

We are writing to inform you that we have not received documentation that your patient, *(insert name)*, has obtained vision monitoring that is required in order to continue receiving SABRIL (vigabatrin). According to the Risk Management and Evaluation Strategy (REMS) program requirements, this patient will need to be tapered off of SABRIL.

Unless verification of vision monitoring is received via the Ophthalmology Assessment Form, your next prescription must be written to taper *(insert name)* off of SABRIL, as no additional refills will be provided following completion of the taper.

This letter serves to remind you of the potential issues surrounding the abrupt withdrawal of SABRIL and provides the medication tapering recommendations from the Withdrawal of Sabril Therapy Section of the approved labeling.

- SABRIL should not be discontinued abruptly and suddenly.
- As with all antiepileptic drugs, SABRIL should be withdrawn gradually to minimize increased seizure frequency.

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- Days 1-3: 100 mg/kg/day (50 mg/kg BID)
- Days 4-6: 50 mg/kg/day (25 mg/kg BID)
- Days 7-10: 25 mg/kg/day (12.5 mg/kg BID)
- Day 11: Vigabatrin completely discontinued

Read the full Prescribing Information in the approved labeling for additional details.

Please provide SHARE Call Center with your patient's Ophthalmology Assessment Form as soon as possible. The Ophthalmology Assessment form is available through S.H.A.R.E. program at www.lundbeckshare.com or the S.H.A.R.E Central Call Center. Please call the S.H.A.R.E call center at 1-888-45-SHARE with any questions, concerns, or updates regarding this patient.

Other medical inquiries should be directed to the Lundbeck Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Lundbeck Patient Safety Department at 1-800-455-1141.

April 7, 2009

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Sincerely,

Lundbeck Inc.

April 7, 2009

Sabril®
vigabatrin
500 mg tablet
500 mg powder for oral solution

PRESCRIBER ENROLLMENT AND AGREEMENT FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

Attestation of Knowledge of Sabril

By signing below and completing the form below and on page 2, I acknowledge that I have read and understand the information in the Sabril Prescribing Information, and I agree to be registered in the SHARE program.

- Sabril is only approved for pediatric patients with infantile spasms (IS) 1 month to 2 years of age or for adults with refractory complex partial seizures (CPS) who have responded inadequately to several alternative treatments. Sabril is not a first-line treatment for refractory CPS.
- I have experience in treating epilepsy.
- I know the risks of Sabril treatment, specifically vision loss.
- *For physicians who prescribe Sabril for IS:* I have knowledge of the risk of T2 MRI abnormality in infants with IS.
- I understand that the effectiveness of Sabril in treating seizures can be assessed within 2 to 4 weeks of initiating therapy in infants and within 12 weeks of initiating therapy in adults. The possibility that vision loss can worsen despite discontinuation of Sabril has not been excluded. In patients with no meaningful improvement in seizure control, Sabril must be discontinued. For patients with meaningful seizure improvement, clinicians and patients need to have continuing discussions of benefit-risk for the duration of therapy.
- I must order and review visual assessment testing at baseline (within 4 weeks of Sabril initiation), at least every 3 months after initiation while on Sabril, and approximately 3 to 6 months after discontinuation of Sabril.
- I will educate patients/parents/legal guardians considering treatment with Sabril on the benefits and risks of the drug, give them a copy of the *Medication Guide*, instruct them to read it, and encourage them to ask questions.
- After reviewing the *Medication Guide* with the patient/parent/legal guardian and prior to the initial prescription, I may use the *Patient/Parent/Legal Guardian-Physician Agreement Form* to reinforce the education provided.
- I will counsel patients who fail to comply with the SHARE program requirements.
- I will remove patients from Sabril therapy who fail to comply with SHARE program requirements after appropriate counseling.
- I understand that Sabril is not available at retail pharmacies. Sabril is only available through select specialty pharmacies.
- I understand that all initial prescriptions for Sabril must go through the SHARE Call Center (1-888-45-SHARE [1-888-457-4273]) and will then be fulfilled by a specialty pharmacy.
- Prior to dispensing any Sabril prescription, I understand that SHARE will verify that I have a signed copy of this *Prescriber Enrollment and Agreement Form* on file.
- I will report all serious adverse events with Sabril to Lundbeck Inc. at 1-800-455-1141 or to the US Food and Drug Administration at 1-800-FDA-1088.

Prescriber Name _____ _____ _____
Last First MI

Prescriber Degree ☐ **MD** ☐ **DO** **Signature** _____ **Date** _____
month/day/year

Attestation continues on page 2

Sabril®
vigabatrin
500 mg tablet
500 mg powder for oral solution

PRESCRIBER ENROLLMENT AND AGREEMENT FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

Attestation continued from page 1

Attestation of Knowledge of Sabril

For additional information, please visit www.LundbeckSHARE.com or call the SHARE Call Center at 1-888-45-SHARE (1-888-457-4273).

Prescriber Name _____

Institution Name (if applicable) _____

Prescriber Address _____ (Street) _____ (City) _____ (State) _____ (ZIP Code)

Telephone Number _____ (Area Code) (Telephone Number)

Alternative Telephone Number _____ (Area Code) (Telephone Number)

Office Fax _____ (Area Code) (Fax Number)

E-mail _____

Prescriber NPI# _____

Specialty

- ☐ **Epileptology**
- ☐ **Pediatric Neurology**
- ☐ **Other** _____
- ☐ **Neurology**
- ☐ **Internal Medicine**

Office Contact Name _____ (Last) _____ (First)

Second Contact Name _____ (Last) _____ (First)

By completing and submitting this form, you will be registered in the SHARE program and may begin prescribing Sabril.

For additional information, please visit www.LundbeckSHARE.com or call the SHARE Call Center at 1-888-45-SHARE (1-888-457-4273).

Once registered in the SHARE program, you will receive a copy of the *Sabril Starter Kit*, which will contain the complete Prescribing Information, information on the SHARE program, the *Medication Guide*, and the *Patient/Parent/Legal Guardian-Physician Agreement* to be used when initiating Sabril therapy. Additional copies of the *Sabril Starter Kit* can be obtained by contacting your Lundbeck Account Manager or contacting the SHARE Call Center (1-888-45-SHARE).

You only need to register in the SHARE program once, and you are under no obligation to prescribe Sabril.

To complete your registration, fax both pages of your completed *Prescriber Enrollment and Agreement Form* to SHARE at 1-877-742-1002.

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

STEP ONE: Patient Profile

Name (First, Middle, Last): _____ Sex: ❑ Male ❑ Female DOB: _____ month/day/year

Address: _____ City: _____ State: _____ Zip Code: _____

SSN: _____-_____-_____ Phone: _____ Today's Date: _____ month/day/year

Sabril Administration Site: ❑ Home ❑ Hospital ❑ I/DD Facility

I authorize my healthcare providers and health plans to disclose personal and medical information related to my use or potential use of Sabril (vigabatrin) to Lundbeck and its agents and contractors and I authorize Lundbeck to use and disclose this information to: 1) establish my benefit eligibility; 2) communicate with my healthcare providers and health plans about my benefit and coverage status and my medical care; 3) provide support services, including facilitating the provision of Sabril to me; 4) evaluate the effectiveness of Sabril's education programs; and 5) participate in the Sabril Patient Registry. I agree that using the contact information I provide, Lundbeck may get in touch with me for reasons related to the SHARE program and may leave messages for me that disclose that I take Sabril.

I understand that once my health information has been disclosed to Lundbeck, privacy laws may no longer restrict its use or disclosure; however, Lundbeck agrees to protect my information by using and disclosing it only for the purposes described above or as required by law. I may also cancel this authorization in the future by notifying Lundbeck in writing and submitting it by fax to 1-877-742-1002 or by calling 1-888-45-SHARE (1-888-457-4273). If I cancel, Lundbeck will cease using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in the SHARE program. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me. I also certify that the information provided about the insurance status is complete and accurate and will update the SHARE Call Center promptly if such status should change.

Power of Attorney: ❑ Yes ❑ No ❑ N/A Power of Attorney (First, Middle, Last): _____

Patient / Parent / Legal Guardian Signature: _____ Date: _____ month/day/year

STEP TWO: Patient Insurance Profile

Name of Primary Payer: _____ Phone Number: _____

Relationship to Cardholder: ❑ Self ❑ Spouse ❑ Child ❑ Other

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Name of Secondary Payer: _____ Phone Number: _____

Relationship to Cardholder: ❑ Self ❑ Spouse ❑ Child ❑ Other

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Prescription Benefit Manager: _____ Phone Number: _____

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

STEP THREE: Prescriber Information

Prescriber's Name (First, Middle Initial, Last): _____ NPI #: _____

Prescriber Address: _____

City: _____ State: _____ Zip: _____

Phone Number: _____ Fax: _____

❑ I have completed the Prescriber Enrollment and Agreement Form required for prescribing Sabril.

I certify that I have reviewed the Medication Guide with the patient/parent/legal guardian, and have counseled him/her on the risks of SABRIL, including vision loss. I commit to ordering and reviewing visual testing at the appropriate intervals in accordance with the SABRIL full prescribing information.

I authorize TheraCom, LLC. in its capacity on behalf of Lundbeck Inc. to be my designated agent and to act as my business associate (as defined in 45 CFR 160.103) to use and disclose any information in this form to the insurer of the above-named patient and to obtain any information about the patient, including any protected health information (as defined in 45 CFR 160.103), from the insurer, including eligibility and other benefit coverage information, for my payment and/or health care operation purposes. As my business associate, TheraCom is required to comply with, and by its signature hereto, agrees that it will comply with, the applicable requirements of 45 CFR 164.504(e) regarding business associates, and that it will safeguard any protected health information that it obtains on my behalf, and will use and disclose this information only for the purposes specified herein or as otherwise required by law.

Prescriber Signature: _____ Date: _____
No Stamped Signature month/day/year

TheraCom Signature: _____ Date: _____
month/day/year

STEP FOUR: Prescription Information

Prescription: Sabril ❑ 500 mg tablets ❑ 500 mg powder for oral solution*† Quantity: _____ (_____) Tablets/Packets
(Digits and written words)

*Child Weight (kg): _____ Date: _____ Refills: _____ (_____)
month/day/year *(Digits and written words)*

SIG: _____

Primary ICD-9 Code: _____ Secondary ICD-9 Code: _____

Instructions: Ship to: ❑ Patient home (address in Step One) ❑ Other (address below) †*Add ancillary supplies as needed*

Patient Name: _____ Address: _____

City: _____ State: _____ Zip: _____ Phone: _____

Consultant ophthalmic professional: _____ Scheduled date of baseline visual assessment _____
month/day/year

Prescriber Signature: _____ Date: _____
month/day/year

Lundbeck

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

STEP FIVE: Patient History

Name (First, Middle, Last):_____ DOB:_____ (month/day/year) Today's Date: _____ (month/day/year)

Race *(Check only one)*: ❑ American Indian or Alaska Native ❑ Asian ❑ Black or African American ❑ Native Hawaiian or Other Pacific Islander ❑ Caucasian ❑ Hispanic ❑ Other

History of Sabril Use:

Is the patient currently taking Sabril? ❑ Yes ❑ No

Has the patient previously taken Sabril? ❑ Yes ❑ No

If the patient has taken or is taking Sabril, how long were they on drug?

_____day(s) (Number) _____week(s) (Number) _____month(s) (Number) _____year(s) (Number)

Reason for Use: ❑ CPS ❑ IS ❑ Other, Specify:_____

If IS, what is the etiology: ❑ Cryptogenic ❑ Symptomatic - TS ❑ Symptomatic, Other

Please check all agents previously or currently utilized by the patient:

Previously Taken	Currently Taking	
❑	❑	Phenytoin
❑	❑	Lamotrigine
❑	❑	Felbamate
❑	❑	Depakote/Valproic acid
❑	❑	Topiramate
❑	❑	Tiagabine
❑	❑	Zonisamide
❑	❑	Levetiracetam
❑	❑	Carbamazepine
❑	❑	Oxcarbazepine
❑	❑	Benzodiazepine(s)
❑	❑	ACTH
❑	❑	Other steroids, specify:_____
❑	❑	OTHER, specify: _____

Please check the # of monotherapy trials by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

Please check the # of trials with 2 agents by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

Please check the # of trials with 3 or more agents by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

www.LundbeckSHARE.com
Fax to 1-877-742-1002

Lundbeck

Sabril®
vigabatrin
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500 mg powder for oral solution

S·H·A·R·E®
Support, Help And Resources for Epilepsy

TREATMENT MAINTENANCE FORM

Because the risk of vision loss increases over time with continued use, it is essential to assess a patient's response to Sabril early and determine that the benefit in treating the patient's seizures with Sabril is clinically meaningful and outweighs the risk of continued therapy with it.

You are therefore asked to attest to the following:

- That you have assessed your patient's response to Sabril
- That you have discussed the benefits and risks of continued Sabril therapy with the patient, parent, and/or legal guardian
- That you have determined in your professional judgment that the benefit of controlling seizures exceeds the risk of vision loss
- That continued Sabril therapy is appropriate and warranted

❑ I have evaluated my patient's clinical response to the recent initiation of Sabril treatment and have verified a clinically meaningful improvement in seizure control. I have determined that the benefit of Sabril treatment outweighs the risk of vision loss at this time. I recommend that my patient continue maintenance therapy with Sabril.

Patient name (First, Middle, Last): _____

Patient DOB: _____
month/day/year

Prescriber name: _____ Prescriber NPI #: _____

Signature: _____ Date: _____
month/day/year

www.LundbeckSHARE.com

Lundbeck

Fax to 1-877-742-1002

Lundbeck Inc., Four Parkway North, Deerfield, IL 60015.

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

OPHTHALMOLOGIC ASSESSMENT FORM

S·H·A·R·E
Support, Help And Resources for Epilepsy

To be completed by the prescribing neurologist with each ophthalmologic assessment.

STEP ONE: Patient Profile

Name (First, Middle, Last) _____ Sex: ❒ Male ❒ Female DOB _____
month/day/year

Address _____ City _____ State _____ ZIP _____

Patient currently on Sabril: ❒ Yes ❒ No

STEP TWO: Consultant Ophthalmic Professional

Ophthalmic Professional Name (First, Middle Initial, Last) _____ NPI #_____

Ophthalmic Professional Address _____

City _____ State_____ ZIP_____

Phone _____

STEP THREE: Ophthalmologic Assessment

Taking into account benefit-risk considerations, the performance of ophthalmologic assessment will be enforced for all patients, and the drug will not continue to be dispensed unless this required documentation is completed and faxed to the SHARE Call Center at 1-877-742-1002.

Section 1

1. Was an ophthalmologic assessment conducted? ❒ Yes _____ ❒ No *(If no, go to Section 2 on next page)*
month/day/year

2. If yes, was a visual acuity evaluation conducted? ❒ Yes ❒ No

What were the results? Left eye _____/_____ Right eye _____/_____

3. Was kinetic perimetry conducted? ❒ Yes ❒ No

What were the results? Degree of retained visual field to V4e target (each eye):

- ❒ >160° retained
- ❒ 120° to 160° retained
- ❒ 60° to <120° retained
- ❒ 40° to <60° retained
- ❒ 20° to <40° retained
- ❒ 10° to <20° retained
- ❒ <10° retained

4. Was static perimetry conducted? ❒ Yes ❒ No

Specify test program used:_____

What were the results? Concentric/partly concentric pattern of decreased sensitivity occurring within:

- ❒ 60°
- ❒ 40°
- ❒ 20°
- ❒ 10°

Assessment form continues on page 2

Assessment form continued from page 1

5. Was OCT conducted? ❒ Yes ❒ No

What were the results? ❒ Normal
❒ Abnormal

6. Was ERG conducted? ❒ Yes ❒ No

What were the results? ❒ Normal
❒ Abnormal

7. Other testing

Specify test:_____

What were the results? ❒ Normal
❒ Abnormal

Section 2

❒ **An ophthalmologic assessment was not conducted on the patient for the following reason(s):**

❒ Patient is blind

❒ Patient's general neurological condition precludes the need for visual assessment

❒ Patient's medical condition prevents visual assessment being performed safely *(please explain)*_____

_____

❒ Other *(please explain)* _____

Section 3

If the assessment occurred more than 1 month after the due date, please indicate the reason:

❒ Patient's financial/reimbursement situation

❒ Transportation issues

❒ Scheduling conflicts

❒ Other *(please explain)* _____

Prescriber's Name _____ *Prescriber's NPI #* _____

Signature _____ *Date* _____
month/day/year

If formal perimetry was conducted, please attach a copy of the visual field recordings.

www.LundbeckSHARE.com Lundbeck ***Fax to 1-877-742-1002***

COMPLEX PARTIAL SEIZURES (CPS)

Patient/Parent/Legal Guardian–Physician Agreement for Sabril® (vigabatrin) Use

Completed forms must be faxed to the SHARE Call Center (1-877-742-1002) at treatment initiation. Place the original signed document in the patient's medical record and provide a copy to the patient, parent, or legal guardian.

Identification of Signer:

Patient—I, _____, am the patient. I am able to read and understand this document and will sign for myself.

Parent/Legal Guardian—I am not the patient. I am the parent/legal guardian of _____, who is the patient. I am able to read and understand this document and will sign on behalf of the patient.

To use Sabril appropriately, the patient/parent/legal guardian should:

- **Be aware that Sabril causes a serious vision problem in some people.**
- **Read the *Medication Guide* to understand the risks of Sabril therapy.**
- **Talk with your doctor about the information you receive before signing the *Patient/Parent/Legal Guardian-Physician Agreement*.**
- **Report any problems you might experience when using Sabril to your doctor as soon as they happen.**
- **Visit the doctor regularly to make sure that Sabril continues to be right for you to take.**

This agreement is to be completed and signed by the patient/parent/legal guardian and the doctor. The person who signs is to read each item below and initial in the space provided if the item is understood. After initialing each item, the signature goes at the end of this agreement. The signer is not to sign this agreement or take Sabril if there are any unanswered questions.

1. I, _____, have read the *Sabril Medication Guide*. My doctor has explained the risks.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

2. I understand that Sabril is a medicine used to treat complex partial seizures that have not responded to several other treatments. The doctor and I have talked about my treatment choices and have decided that treatment with Sabril is right for me.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

3. I understand that about 1 in 3 adult patients taking Sabril have damage to their vision. I understand that if any vision loss occurs, it will not improve even if Sabril is stopped.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

4. I understand that there is no way to tell if I will develop vision loss.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

5. I understand that vision tests required by the doctor when starting Sabril treatment must be obtained. This testing will continue as long as Sabril is taken and after stopping therapy. I understand that these tests will not prevent vision loss. However, by stopping the treatment as a result of these tests, the amount of vision loss may be limited. I understand that it is important to see the doctor on a regular basis to make sure that Sabril continues to be right for me to take.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

6. The doctor and I have talked about my epilepsy. We have also talked about the potential benefits and risks of taking Sabril. We have agreed that Sabril therapy will be started, and that the initial treatment with Sabril will consist of an Evaluation Phase of about 3 months.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

7. If the seizures <u>are not</u> better during the Evaluation Phase, Sabril® (vigabatrin) therapy must be stopped. If seizure control has improved, I will discuss with the doctor the potential benefits and risks of continuing Sabril therapy (the Maintenance Phase). I understand that the risk of vision loss will continue as long as I continue to take Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

8. I understand that Sabril will be prescribed for myself, my son or daughter, or my legal ward only. I will not share Sabril with other people.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

9. The doctor has discussed with me other treatments for my epilepsy. We have decided that Sabril is the right treatment for me. I understand that Sabril can be discontinued at any time. I also know that I cannot stop taking Sabril without my doctor telling me to do so. I agree to tell the doctor if I decide to stop taking Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

10. All my questions were answered to my satisfaction. I now authorize the doctor, _____, to begin treatment with Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

I have read and understood all of the information presented above and agree to use Sabril therapy.

Patient/Parent/Legal Guardian Agreement

Evaluation Phase

To be signed by patient/parent/legal guardian upon initiation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Maintenance Phase

To be signed by patient/parent/legal guardian upon continuation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Physician Agreement

I, _____, have fully explained to the patient/parent/legal guardian the potential benefits and risks of Sabril treatment. I have provided the patient/parent/legal guardian with the brochure entitled *Sabril Medication Guide*, and have answered all questions regarding therapy with Sabril.

Evaluation Phase

To be signed by physician upon initiation of Sabril therapy.

Signature:_____ Date_____ (month/day/year)

Maintenance Phase

To be signed by physician upon continuation of Sabril maintenance therapy.

Signature:_____ Date_____ (month/day/year)

Fax to the SHARE Call Center (1-877-742-1002)

INFANTILE SPASMS (IS)

Parent/Legal Guardian–Physician Agreement for Sabril® (vigabatrin) Use

Completed forms must be faxed to the SHARE Call Center (1-877-742-1002) at treatment initiation. Place the original signed document in the patient's medical record and provide a copy to the patient, parent, or legal guardian.

To use Sabril appropriately, you should:

- **Be aware that Sabril causes a serious vision problem in some people.**
- **Be aware that there have been reports of changes in the brain images of some patients with infantile spasms on Sabril. The importance of these changes is not known.**
- **Read the *Medication Guide* to understand the risks of Sabril therapy.**
- **Talk with your doctor about the information you receive before signing the *Parent/Legal Guardian-Physician Agreement*.**
- **Report any problems your infant might experience when using Sabril to your infant's doctor as soon as they happen.**
- **Visit your infant's doctor regularly to make sure that Sabril continues to be right for your infant to take.**

This agreement is to be completed and signed by the parent/legal guardian and the doctor. Read each item below and initial in the space provided if you understand the item. After you have initialed each item, sign your name at the end of this agreement. Do not sign this agreement or have your infant take Sabril if you have any unanswered questions.

1. I, _____, have read the *Sabril Medication Guide*. My infant's doctor has explained the risks.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

2. I understand that Sabril is a medicine used to treat infantile spasms. My infant's doctor and I have talked about my infant's treatment. We both think that Sabril should be used to treat my infant.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

3. I understand that about 1 in 3 infants taking Sabril will have damage to their vision. I understand that if any vision loss occurs, it will not improve even if my infant stops taking Sabril.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

4. I understand that there is no way to tell if my infant will develop vision loss.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

5. I understand that vision tests required by my infant's doctor when starting Sabril treatment must be obtained for my infant. This testing will continue as long as Sabril is taken and after stopping therapy. I understand that these tests will not prevent vision loss. However, by stopping the treatment as a result of these tests, the amount of vision loss may be limited. I understand that it is important to take my infant to see his or her doctor on a regular basis to make sure that Sabril continues to be right for them to take.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

6. I understand that there have been reports of a change in the brain pictures of infants taking Sabril. The change may reverse by itself or when the Sabril dose is lowered or is stopped. It is not known if this change has any effect on the infant.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

7. I understand that my infant's doctor may want to take an MRI or picture of my infant's brain before starting or during Sabril treatment.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

8. My infant's doctor and I have talked about my infant's epilepsy. We have talked about Sabril® (vigabatrin) as a treatment option for my infant. We have agreed that Sabril therapy will be started, and that the initial treatment with Sabril will consist of an Evaluation Phase of about 1 month.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

9. If my infant's seizures <u>are not</u> better during the Evaluation Phase, Sabril therapy must be stopped. If my infant's seizure control has improved, I will discuss with his or her doctor the potential benefits and risks of continuing Sabril therapy (the Maintenance Phase). I understand that the risk of developing vision loss will continue as long as my infant takes Sabril. I also understand that there may be some chance of an MRI change seen in the brain; however, we do not know if this change has any medical significance.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

10. Sabril will be prescribed only for my infant. I will not share his or her Sabril with other people.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

11. We have decided that Sabril is the most appropriate treatment for my infant. I understand that my infant can stop taking Sabril at any time. However, I will not have my infant abruptly stop using Sabril unless instructed to do so by his or her doctor. If treatment is abruptly stopped, my infant's seizures might increase or return. I agree to tell my doctor if I decide to stop giving Sabril to my infant.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

12. All my questions were answered to my satisfaction. I now authorize my doctor, _____, to begin my infant's treatment with Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

I have read and understood all of the information presented above and agree to use Sabril therapy.

Parent/Legal Guardian Agreement

Evaluation Phase

To be signed by parent/legal guardian upon initiation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Maintenance Phase

To be signed by parent/legal guardian upon continuation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Physician Agreement

I, _____, have fully explained to the parent/legal guardian the potential benefits and risks of Sabril treatment. I have provided the parent/legal guardian with the brochure entitled *Sabril Medication Guide*, and have answered all questions regarding therapy with Sabril.

Evaluation Phase

To be signed by physician upon initiation of Sabril therapy.

Signature:_____ Date_____ (month/day/year)

Maintenance Phase

To be signed by physician upon continuation of Sabril maintenance therapy.

Signature:_____ Date_____ (month/day/year)

Fax to the SHARE Call Center (1-877-742-1002)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
08/21/2009

Hoefler, Carol

From: Katz, Julie
Sent: Monday, October 19, 2009 2:47 PM
To: Mizerk, Don; Michael Brophy
Cc: KeiAna Sanderlin; Hoefler, Carol; Tokarz, Aubrey
Subject: RE: Novartis v Anchen

Mike, I sent the document to Judy and she's got the instructions to get it filed. I am informed that she'll handle changing the caption for the Certificate of Interested Party as well. Nothing's changed since we did the one(s) in the Eurand v Anchen case.

Best to all, Julie

From: Mizerk, Don
Sent: Monday, October 19, 2009 2:43 PM
To: Michael Brophy; Katz, Julie
Cc: KeiAna Sanderlin; Hoefler, Carol; Mizerk, Don
Subject: RE: Novartis v Anchen

Mike,

I signed the engagement letter and my assistant is sending you a pdf/mail confirmation.

I assume you and Julie have the extension motion nailed down since we need to have that on file today.

Thanks and let me know if you have any questions.

Don

-----Original Message-----
From: Michael Brophy [mailto:mbrophy@raklaw.com]
Sent: Friday, October 16, 2009 6:12 PM
To: Katz, Julie; Mizerk, Don
Cc: KeiAna Sanderlin
Subject: Re: Novartis v Anchen

Julie and Don,

Thank you for asking Russ, August & Kabat to serve as local counsel in another matter for Anchen. There does not appear to be a conflict with us defending Achen in the California Enablix litigation brought by Novartis. Attached is the engagement letter. As this is anticipated to be a small matter, my firm will not require an initial retainer.

Have a good weekend,

Mike

Michael S. Brophy, Esq.
Russ August & Kabat
12424 Wilshire Blvd., 12th Floor
Los Angeles, CA 90025
310-826-7474
310-826-6991 (fax)
mbrophy@raklaw.com

On Friday, October 16, 2009 2:55 PM, Katz, Julie <Julie.Katz@huschblackwell.com> wrote:
>Michael, Judy: Here's the Complaint in Novartis v Anchen.
>
>
>Julie A. Katz
>Partner

>Husch Blackwell Sanders Welsh & Katz
>120 South Riverside Plaza
>Suite 2200
>Chicago, IL 60606
>Direct Phone: 312.655.1500
>Direct Fax: 312.655.1501
>E-Mail: julie.katz@huschblackwell.com
>Website: www.huschblackwell.com
>
>
>The Richard Linn American Inn of Court, 2009-2010 Treasurer The Chicago
>IP Alliance, 2009-2010 Vice President National Association of Women
>Business Owners, Corporate Partner
>
>
>
>****** Begin Notice from Husch Blackwell Sanders LLP ******
>
>Pursuant to U. S. Treasury regulations, we inform you that any federal
>tax advice contained in this message (including all constituent email
>correspondence, attachments, enclosures and/or exhibits) is not
>intended or written to be used, and cannot be used, for the purpose of
>(i) avoiding penalties under the Internal Revenue Code or (ii)
>promoting, marketing or recommending to another party any transaction
>or matter addressed herein.
>
>******* End Notice from Husch Blackwell Sanders LLP *******
>
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-006

NDA APPROVAL

Lundbeck Inc.
Attention: Jenny Swalec, Sr. Director
Global Regulatory Affairs
4 Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your new drug application (NDA) dated October 17, 2006, received October 18, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (vigabatrin) for Oral Solution, 500 mg.

We acknowledge receipt of your additional correspondence and amendments dated:

December 28, 2007	February 12, 2008	March 14, 2008	April 15, 2008
April 23, 2008	April 25, 2008	May 2, 2008	May 6, 2008
May 7, 2008	May 14, 2008	May 15, 2008	May 16, 2008
May 23, 2008	May 27, 2008	May 29, 2008	June 2, 2008
June 2, 2008	June 4, 2008	June 6, 2008	June 6, 2008
June 11, 2008	June 18, 2008	June 20, 2008	June 26, 2008
July 14, 2008	July 17, 2008	July 23, 2008	August 4, 2008
September 26, 2008	October 31, 2008	November 26, 2008	December 24, 2008
January 12, 2009	January 30, 2009	February 5, 2009	February 24, 2009
March 10, 2009	March 25, 2009	April 2, 2009	April 9, 2009
April 21, 2009	April 24, 2009	June 22, 2009	July 7, 2009
July 14, 2009	July 29, 2009	August 13, 2009	August 17, 2009
August 18, 2009	August 19, 2009		

The December 28, 2007, submission constituted a resubmission to our April 5, 2007, Refusal to File letter.

This new drug application provides for the use of Sabril (vigabatrin) for Oral Solution for Infantile Spasms.

We have completed our review of this application, as amended and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because Sabril (vigabatrin) for Oral Solution for the treatment infantile spasms has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of potential toxicity due to the increased plasma concentrations that may occur in younger infants, to assess a signal of a serious risk of neurotoxicity, or to assess the known serious risk of vision loss.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1523-1: A toxicology study in the juvenile rat examining the potential for vigabatrin exposure during development to produce neuronal damage. The study protocol should be submitted to the Division for comment prior to study initiation.

Final Protocol Submission:	by July 2010
Study Completion Date:	by September 2011
Final Report Submission:	by March 2012

1523-2: A juvenile animal toxicity study of vigabatrin in a non-rodent species. The study protocol should be submitted to the Division for comment prior to study initiation.

Final Protocol Submission:	by September 2012
Study Completion Date:	by March 2014
Final Report Submission:	by September 2014

1523-3: A study examining the protective effect of taurine on vigabatrin-induced retinal damage in rodent, as reported by Jammoul *et al.* (Jammoul A F *et al. Ann Neurol* 65:98-107, 2009), but administering vigabatrin by the oral route. An attempt should be made to induce

retinal toxicity in pigmented animals by, for example, exposing them to high intensity light for an appropriate duration following induction of mydriasis (cf. Rapp LM, Williams TP *Vision Res* 20:1127-1131, 1980). If this is successful, the study should be conducted in both albino and pigmented animals. The final study protocol should be submitted to the Agency for comment prior to study initiation.

Final Protocol Submission:	by January 2010
Study Completion Date:	by June 2011
Final Report Submission:	by November 2011

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of potential toxicity because of the increased plasma concentrations that may occur in younger infants.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1523-4: An open label clinical trial to assess the single and multiple dose (at steady state) pharmacokinetics of Sabril (vigabatrin) at a clinically relevant dose in infants with infantile spasms who are 1-5 months of age.

Final Protocol Submission:	by January 2010
Study Completion Date:	by July 2013
Final Report Submission:	by March 2014

Submit the protocols to your IND for this product with a cross-reference letter to this NDA. Submit all final reports to this NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS REPORTABLE UNDER SECTION 506B

We remind you of your postmarketing study commitment agreed to in your communication dated August 19, 2009. You commit to conduct the following:

1523-5: An adequately controlled trial in infants treated with Sabril (vigabatrin) for infantile spasms to further characterize the minimum duration of therapy required for sustained suppression of spasms. It is possible that a shorter duration of therapy will mitigate the risk of vision damage. The protocol for the trial should be discussed with the Agency prior to being submitted as a special protocol assessment (SPA).

Final Protocol Submission:	July 2010
Study Completion Date:	July 2013
Final Report Submission:	March 2014

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Commitment Protocol,**" "**Postmarketing Commitment Final Report,**" or "**Postmarketing Commitment Correspondence.**"

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Sabril (vigabatrin) to ensure the benefits of the drug outweigh the risks of vision loss and of suicidal thoughts and behaviors.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Sabril (vigabatrin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Sabril (vigabatrin). FDA has determined that Sabril (vigabatrin) is a product for which patient labeling could help prevent serious adverse effects. Sabril also has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect their decisions to use, or continue to use Sabril (vigabatrin). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Sabril (vigabatrin).

We have also determined that a communication plan is necessary to support implementation of the REMS. The communication plan should be implemented at product launch (the first six months after product approval) and continued for three years.

Pursuant to 505-1(f)(1), we have also determined that Sabril (vigabatrin) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate these risks listed in the labeling. The elements to assure safe use will mitigate the risk of Sabril (vigabatrin)-induced vision loss by ensuring that patients receive appropriate monitoring of vision, and by ensuring that Sabril (vigabatrin) therapy is discontinued in patients who experience inadequate clinical response.

Your proposed REMS, submitted on August 18, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS Assessment Plan should include, but is not limited to, the following:

1) Registration and drug distribution data

2) Medication Guide assessment data
   a) Patients' understanding of the serious risks of Sabril (vigabatrin)
   b) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
   c) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

3) Report of mandatory benefit-risk assessments prior to entering maintenance therapy, including how many patients completed the mandatory benefit-risk assessment, and how many patients did not complete the mandatory benefit-risk assessment.

4) Vision Monitoring

5) Patient/Parent or Legal Guardian Knowledge, Attitude and Behavior (KAB) Surveys

6) Ophthalmic professional KAB Surveys

7) Prescriber KAB Surveys

Additional details for the REMS assessment plan are in Appendix I.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

The requirements for assessments of an approved REMS also include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-006 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-006
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22-006
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-006."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to carton and immediate container labels submitted on August 13, 2009 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

(October 2005). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 22-006." Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Tamy Kim, PharmD, Senior Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Appendix I, Labeling and REMS

Appendix I: REMS Assessment Plan

1) Registration and drug distribution data
   a) Report of Sabril (vigabatrin) distribution;
   b) The number of patients registered for the reporting period and cumulatively, including the age and gender of the patients;
   c) The number and specialties of prescribers registered for the reporting period and cumulatively;
   d) The number of patients who discontinue Sabril (vigabatrin) therapy before the beginning of the maintenance phase;
   e) The number of patients whose therapy is interrupted because of changing prescribers.
   f) The number of prescribers who are de-registered and reasons;
   g) The number of prescribers who are re-registered and reasons;
   h) The number of patients who are de-registered and reasons;
   i) The number of Sabril (vigabatrin) shipments to patients without prior authorization from Lundbeck Inc.; and
   j) The number of pharmacies who are de-enrolled, with reasons for de-enrollment.

2) Medication Guide assessment data
   a) Patients' understanding of the serious risks of Sabril (vigabatrin)
   b) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
   c) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

3) Report of mandatory benefit-risk assessments prior to entering maintenance therapy, including how many patients completed the mandatory benefit-risk assessment, and how many patients did not complete the mandatory benefit-risk assessment.

4) Vision Monitoring
   a) Frequency distribution of number of reminder calls for vision monitoring made per patient;
   b) Review of pattern of reminder calls to confirm no gap in therapy;
   c) The number of patients who miss vision monitoring appointments, the reason they miss them, and how long the monitoring is delayed;
   d) The number and percent of patients who obtain baseline vision monitoring within the first 2 weeks and within the first 4 weeks of treatment initiation, age, and prescriber;
   e) The number and percent of patients who do not obtain baseline vision monitoring within the first 4 weeks after treatment initiation, by reason, age, and prescriber;
   f) The number of patients who are at least 60 days late in obtaining required vision monitoring appointments on 3 separate occasions;
   g) The number of patients by age who do not complete the required vision monitoring within the REMS assessment period;

h) The number of patients who are exempted from vision monitoring by reason checked on the Ophthalmologic Assessment Form and by prescriber;
i) Narrative summary and analysis of information collected on Ophthalmologic Assessment Forms; and
j) Narrative summary and assessments of reports of vision loss.

5) Patient/Parent or Legal Guardian Knowledge, Attitude and Behavior (KAB) Surveys
   a) Number of patients, parents, and legal guardians who call to volunteer for survey participation;
   b) Number of patients who meet inclusion criteria;
   c) Description of survey participants;
      i) Indication for Sabril (vigabatrin) use;
      ii) Duration of use (as indicated in SHARE database);
      iii) Gender;
      iv) Age;
      v) Geographic region;
      vi) Status (patient, parent, legal guardian); and
      vii) Where treated.
   d) Frequency distribution of responses to each question; that is, the number of respondents who give each answer to each question;
   e) Percent of those answering each response to each question in total and separately for patients and caregivers;
   f) Percent of respondents indicating correct response to each objective in total and separately for patients and caregivers;
   g) Analyses will be stratified by indication for Sabril (vigabatrin) use as well as analyses for the combined sample;
   h) Level of understanding of Sabril (vigabatrin) risks as measured by the score on the KAB survey;
   i) Number and percent of respondents in patient/parent/legal guardian KAB survey who report reading the Medication Guide; and
   j) Number and percent of respondents in the patient/parent/legal guardian KAB survey who report they receive a Medication Guide with each prescription.

6) Ophthalmic professional KAB Surveys
   a) The number of ophthalmic professionals in the sample, in total, and by key characteristics;
   b) The number of ophthalmic professionals attempted to contact at each wave; of those attempted to contact:
      i) The number who opt out/ask to be removed from list;
      ii) The number who agree to participate in the survey;
      iii) Of those who agree to participate, number who qualify;
      iv) Of those who qualify, number who complete any portion of the interview; and

v) Of those who qualify, number who complete the survey.

c) Description of survey participants
   i) Experience with Sabril (vigabatrin); and
   ii) Geographic region.
d) Frequency distribution of responses to each question;
e) Percent of those answering each response to each question; and
f) Percent of respondents indicating correct response to each objective.

7) Prescriber KAB Surveys
   a) The number of physicians in the sample, in total, and by key characteristics;
   b) The number of physicians you attempted to contact at each wave; of those you attempted to contact:
      i) Number who opt out/ask to be removed from list;
      ii) Number who agree to participate in the survey;
      iii) Of those who agree to participate, number who qualify;
      iv) Of those who qualify, number who complete any portion of the interview;
      v) Of those who qualify, number who complete the survey;
      vi) Description of survey participants;
         (1) Medical specialty and whether adult or pediatric practice;
         (2) Experience with Sabril (vigabatrin); and
         (3) Geographic region.
      vii) Frequency distribution of responses to each question;
      viii) Percent of those answering each response to each question; and
      ix) Percent of respondents indicating correct response to each objective; and
   c) Additional analyses, included subset by adult or pediatric practice, if needed.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SABRIL safely and effectively. See full prescribing information for SABRIL.

SABRIL® (vigabatrin) for Oral Solution
For Oral Administration Only
Initial U.S. Approval: Pending **℞ Only**

WARNING: VISION LOSS
See full prescribing information for complete boxed warning

- SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity.
- Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss
- Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL
- Periodic vision testing is required for patients on SABRIL, but cannot reliably prevent vision damage
- Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program

----------INDICATIONS AND USAGE----------
SABRIL is an antiepileptic drug (AED) indicated for:
- **Infantile Spasms (IS) - 1 Month to 2 Years of Age** (1.1)

----------DOSAGE AND ADMINISTRATION----------
- Infantile Spasms: Initiate therapy at 50 mg/kg/day twice daily increasing total daily dose per instructions to a maximum of 150 mg/kg/day (2.1)
- Dose adjustment recommended in renally impaired patients (2.2)
- Reduce dose gradually upon discontinuation (2.3)

----------DOSAGE FORM AND STRENGTHS----------
Powder for Oral Solution: 500 mg (3.1)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- SABRIL causes permanent vision loss (5.1)
- Abnormal MRI signal changes have been reported in some infants with IS receiving SABRIL (5.3)
- Antiepileptic drugs, including SABRIL, increase the risk of suicidal thoughts and behavior (5.5)
- Dose should be tapered gradually to avoid withdrawal seizures (5.6)
- SABRIL causes anemia (5.7)
- SABRIL causes somnolence and fatigue (5.8)
- SABRIL causes peripheral neuropathy (5.9)
- SABRIL causes weight gain (5.10)
- SABRIL causes edema (5.11)

----------ADVERSE REACTIONS----------
Most common adverse reactions described in adults (change of ≥5% over placebo) in addition to permanent vision loss in adult controlled trials with vigabatrin were fatigue, somnolence, nystagmus, tremor, vision blurred, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck Inc. at 1-800-455-1141 or www.lundbeckinc.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Decreased phenytoin plasma levels have been reported (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available(8.1)
- Nursing Mothers: SABRIL is excreted in human milk (8.2)
- Renal Impairment: Dose adjustment recommended (2.2, 8.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

Issued: 08/07/09

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: VISION LOSS

- SABRIL causes permanent vision loss in infants, children and adults. Because assessing vision loss is difficult in children, the frequency and extent of vision loss in infants and children is poorly characterized. For this reason, the data described below is primarily based on the adult experience.
- In adults, SABRIL causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss
- It is possible that vision loss can worsen despite discontinuing SABRIL
- Because of the risk of vision loss, SABRIL should be withdrawn from patients with infantile spasms who fail to show substantial clinical benefit within 2 to 4 weeks of initiation, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.
- In infants and children, vision loss may not be detected until it is severe. Nonetheless, vision should be assessed to the extent possible at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy. Once detected, vision loss due to SABRIL is not reversible. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy
- Symptoms of vision loss from SABRIL are unlikely to be recognized by the parent or caregiver before vision loss is severe. Vision loss of milder severity, although unrecognized by the caregiver, may still adversely affect function.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks
- The lowest dose and shortest exposure to SABRIL should be used that is consistent with clinical objectives
- The possibility that vision loss from SABRIL may be more common, more severe or have more severe functional consequences in infants and children than in adults cannot be excluded

Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program called SHARE, by calling 1-888-45-SHARE. Only prescribers and pharmacies registered with SHARE may prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE [see WARNINGS AND PRECAUTIONS, Distribution Program for SABRIL (5.2)].

1 INDICATIONS AND USAGE

1.1 Infantile Spasms (1 Month to 2 Years of Age)

SABRIL® is indicated as monotherapy for pediatric patients with infantile spasms (IS) for whom the potential benefits outweigh the potential risk of vision loss [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Infantile Spasms (1 Month to 2 Years of Age)

Physicians should review and discuss the Medication Guide with the caregiver(s) prior to preparation and administration of SABRIL. Physicians should confirm that caregiver(s) understand how to reconstitute SABRIL and to administer the correct dose to their infants.

SABRIL should be given as twice daily oral administration with or without food. The initial dosing is 50 mg/kg/day given in two divided doses and can be titrated by 25-50 mg/kg/day increments every 3 days up to a maximum of 150 mg/kg/day [see USE IN SPECIFIC POPULATIONS, Pediatric Use (8.3)].

The entire contents of the appropriate number of packets (500 mg/packet) of powder should be emptied into an empty cup, and should be dissolved in 10 mL of cold or room temperature water per packet using the 10 mL oral syringe supplied with the medication. The concentration of the final solution is 50 mg/mL. Table 1 below describes how many packets and how many mL of water will be needed to prepare each individual dose. Each individual dose should be prepared immediately before use and administered cold or at room temperature.

Table 1. Number of Packages and mL of Water used for Each Individual Dose

Each Individual Dose (Prepared and Given Twice Daily)	Number of Packets	Number of mL of Water for Dissolving
0 to 500 mg	1 packet	10 mL
501 to 1000 mg	2 packets	20 mL
1001 to 1500 mg	3 packets	30 mL

Table 2 provides the volume that should be administered as individual doses in infants of various weights is presented below:

Table 2. Infant Dosing Table

Weight (kg)	Starting Dose 50 mg/kg/day	Maximum Dose 150 mg/kg/day
3	1.5 mL twice daily	4.5 mL twice daily
4	2 mL twice daily	6 mL twice daily
5	2.5 mL twice daily	7.5 mL twice daily
6	3 mL twice daily	9 mL twice daily
7	3.5 mL twice daily	10.5 mL twice daily

Table 2. Infant Dosing Table

8	4 mL twice daily	12 mL twice daily
9	4.5 mL twice daily	13.5 mL twice daily
10	5 mL twice daily	15 mL twice daily
11	5.5 mL twice daily	16.5 mL twice daily
12	6 mL twice daily	18 mL twice daily
13	6.5 mL twice daily	19.5 mL twice daily
14	7 mL twice daily	21 mL twice daily
15	7.5 mL twice daily	22.5 mL twice daily
16	8 mL twice daily	24 mL twice daily

2.2 Patients with Renal Impairment

SABRIL is primarily eliminated through the kidney. Information about how to adjust the dose in pediatric patients with renal impairment is unavailable.

The following dose adjustments are pertinent to the possible use of this dosage form in adults with renal impairment:

In patients with mild renal impairment (CLcr >50 to 80 mL/min), the dose should be decreased by 25%; in patients with moderate renal impairment (CLcr >30 to 50 mL/min), the dose should be decreased by 50%; and in patients with severe renal impairment (CLcr >10 to <30 mL/min), the dose should be decreased by 75%.

CLcr in mL/min may be estimated from a serum creatinine (mg/dL) determination using the following formula:

CLcr *= [140-*age* (*years*)] *weight* (*kg*)/72 *serum creatinine* (*mg/dL*)]
*[0.85 *for female patients*]

The effect of dialysis on SABRIL clearance has not been adequately studied.

[see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5)].

2.3 General Dosing Considerations

Monitoring of SABRIL plasma concentrations to optimize therapy is not helpful. If a decision is made to discontinue SABRIL, the dose should be gradually reduced. In a controlled clinical study in patients with IS, vigabatrin was tapered by decreasing the dose at a rate of 25-50 mg/kg every 3-4 days [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6)].

3 DOSAGE FORMS AND STRENGTHS

3.1 Powder for Oral Solution

500 mg Packet.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Vision Loss (see BOXED WARNING)

Because of the risk of vision loss and because SABRIL, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 2 to 4 weeks of initiation of treatment, should be withdrawn from SABRIL. If in the clinical judgment of the prescriber evidence of treatment failure becomes obvious earlier than 2 to 4 weeks, treatment with SABRIL should be discontinued at that time. Patient response to and continued need for treatment should be periodically assessed.

Monitoring of Vision

Because vision testing in infants and children is difficult, vision loss may not be detected until it is severe. However, monitoring of vision by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina, must be performed at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. This assessment should include visual acuity and visual field whenever possible.

The diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor vision periodically must be documented under the SHARE program. In patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate caregiver(s) counseling, and with documentation in the SHARE program of the inability to test vision. Because of variability, results from ophthalmic monitoring must be interpreted with caution, and repeat testing is recommended if results are abnormal or uninterpretable.

The onset and progression of vision loss from SABRIL is unpredictable, and may occur or worsen precipitously. Once detected, vision loss due to SABRIL is not reversible.

5.2 Distribution Program for SABRIL

SABRIL is available only under a special restricted distribution program called the SHARE program. Under the SHARE program, only prescribers and pharmacies registered with the program are able to prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE. Contact the SHARE program at 1-888-45-SHARE.

To enroll in SHARE, prescribers must understand the risks of SABRIL and complete the SHARE Prescriber Enrollment and Agreement Form indicating agreement to:

- Enroll all patients in SHARE
- Review the SABRIL Medication Guide with every caregiver
- Educate caregiver(s) on the risks of SABRIL, including the risk of vision loss [see BOXED WARNING: VISION LOSS]
- Arrange for visual field and retinal exam by an expert examiner and review visual evaluation prior to initiation of SABRIL treatment and every 3 months during therapy
- Remove patients from SABRIL therapy if the patients do not experience a meaningful reduction in seizures
- Counsel caregiver(s) who fail to comply with the program requirements
- Remove patients from SABRIL therapy whose caregiver(s) fail to comply with the program requirements after appropriate counseling

5.3 Magnetic Resonance Imaging (MRI) Abnormalities

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with SABRIL. In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 21.5% in SABRIL treated patients versus 4.1% in patients treated with other therapies.

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment. In a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied.

Neurotoxicity (including convulsions and hypomyelination) was observed in rats exposed to vigabatrin during late gestation and the neonatal and juvenile periods of development. The relationship between these findings and the abnormal MRI findings in infants treated for IS with vigabatrin is unknown [see WARNINGS AND PRECAUTIONS, Neurotoxicity (5.4) and USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)].

The specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with vigabatrin for refractory complex partial seizures (CPS). In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo patients.

5.4 Neurotoxicity

Vacuolization, characterized by fluid accumulation and separation of the outer layers of myelin, has been observed in brain white matter tracts in adult and juvenile rats and adult mice, dogs, and possibly monkeys following administration of vigabatrin. This lesion, referred to as intramyelinic edema (IME), was seen in animals at doses within the human therapeutic range. A no-effect dose was not established in rodents or dogs. In the rat and dog, vacuolization was reversible following discontinuation of vigabatrin treatment, but, in the rat, pathologic changes consisting of swollen or degenerating axons, mineralization, and gliosis were seen in brain areas in which vacuolation had been previously observed. Vacuolization in adult animals was correlated with alterations in MRI and changes in visual and somatosensory evoked potentials (EP).

Administration of vigabatrin to rats during the neonatal and juvenile periods of development produced vacuolar changes in the gray matter (areas including the thalamus, midbrain, deep cerebellar nuclei, substantia nigra, hippocampus, and forebrain) which are considered distinct from the IME observed in vigabatrin treated adult animals. Decreased myelination, retinal dysplasia, and neurobehavioral abnormalities (convulsions, neuromotor impairment, learning deficits) were also observed following vigabatrin treatment of young rats. These effects occurred at doses associated with plasma vigabatrin levels substantially lower than those achieved clinically in infants and children.

In a published study, vigabatrin (200, 400 mg/kg/day) induced apoptotic neurodegeneration in the brain of young rats when administered by intraperitoneal injection on postnatal days 5-7.

Administration of vigabatrin to female rats during pregnancy and lactation at doses below those used clinically resulted in hippocampal vacuolation and convulsions in the mature offspring.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3)].

5.5 Suicidal Behavior and Ideation

The following information is pertinent to the possible use of this dosage form in adults. Antiepileptic drugs (AEDs), including SABRIL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing SABRIL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregiver(s), and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to

be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, SABRIL should be withdrawn gradually.

Caregivers should be told not to suddenly discontinue SABRIL therapy. In a controlled clinical study in patients with IS, vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days [see DOSAGE AND ADMINISTRATION, General Dosing Consideration (2.3), PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.5)].

5.7 Anemia

In North American controlled trials in adults, 5.7% of patients (16/280) receiving SABRIL and 1.6% of patients (3/188) receiving placebo had adverse events of anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled trials, there were mean decreases in hemoglobin of about 3% and 0% in SABRIL and placebo-treated patients, respectively, and in hematocrit of about 1% in Sabril treated patients compared to a gain of about 1% in patients treated with placebo.

In controlled and open label epilepsy trials in adults and pediatric patients, 3 SABRIL patients (0.06%, 3/4855) discontinued for anemia and 2 SABRIL patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or hematocrit below 24%.

5.8 Somnolence and Fatigue

SABRIL causes somnolence and fatigue. Patients should be advised not to drive a car or operate other complex machinery until they are familiar with the effects of SABRIL on their ability to perform such activities.

Pooled data from two SABRIL controlled trials in adults demonstrated that 24% (54/222) of SABRIL patients experienced somnolence compared to 10% (14/135) of placebo patients. In those same studies, 28% of SABRIL patients experienced fatigue compared to 15% (20/135) of placebo patients. Almost 1% of SABRIL patients discontinued from clinical trials for somnolence and almost 1% discontinued for fatigue.

5.9 Peripheral Neuropathy

SABRIL has been shown to cause symptoms of peripheral neuropathy in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not these symptoms occur in the pediatric population.

In a pool of North American controlled and uncontrolled epilepsy studies, 4.2% (19/457) of SABRIL treated patients developed signs and/or symptoms of peripheral neuropathy. In the subset of North American placebo controlled epilepsy trials, 1.4% (4/280) of SABRIL treated patients and no (0/188) placebo patients developed signs and/or symptoms of peripheral neuropathy. Initial manifestations of peripheral neuropathy in these trials included, in some combination, symptoms of numbness or tingling in the toes or feet, signs of reduced distal lower limb vibration or position sensation, or progressive loss of reflexes, starting at the ankles. Clinical studies in the development program were not designed to investigate peripheral neuropathy systematically and did not include nerve conduction studies, quantitative sensory testing, or skin or nerve biopsy. There is insufficient evidence to determine if development of theses signs and symptoms were related to duration of SABRIL treatment, cumulative dose, or if the findings of peripheral neuropathy were completely reversible upon discontinuation of SABRIL.

5.10 Weight Gain

SABRIL has been shown to cause weight gain in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not weight gain occurs in the pediatric population.

Data pooled from randomized controlled trials found that 17% (77/443) of SABRIL patients gained ≥7% of baseline body weight versus 8% (22/275) of placebo patients. In these same trials, the mean weight change among SABRIL patients was 3.5 kg compared to 1.6 kg for placebo patients. In all epilepsy trials, 0.6% (31/4855) of SABRIL patients discontinued for weight gain. The long term effects of SABRIL related weight gain are not known. Weight gain was not related to the occurrence of edema.

5.11 Edema

SABRIL has been shown to cause edema in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not edema occurs in the pediatric population.

Pooled data from controlled trials demonstrated increased risk among SABRIL patients compared to placebo patients for peripheral edema (SABRIL 2%, placebo 1%), and edema (SABRIL 1%, placebo 0%). In these studies, one SABRIL and no placebo patients discontinued for an edema related AE. There was no apparent association between edema and cardiovascular adverse events such as hypertension or congestive heart failure. Edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

6 ADVERSE REACTIONS

SABRIL causes permanent damage to vision in a high percentage of patients [see BOXED WARNING: VISION LOSS and WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Events in U.S. and Primary Non-U.S. Clinical Studies

In U.S. and primary non-U.S. clinical studies of 3139 adult and 999 pediatric patients treated with SABRIL, the most commonly observed (≥5%) adverse events associated with the use of SABRIL in combination with other AEDs were headache (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsion (11%), nasopharyngitis (10%), weight increased (10%), upper respiratory tract infection (10%), visual field defect (9%), depression (8%), tremor (7%), nystagmus (7%), nausea (7%), diarrhea (7%), memory impairment (7%), insomnia (7%), irritability (7%), coordination abnormal (7%), vision blurred (6%), diplopia (6%), vomiting (6%), influenza (6%), pyrexia (6%), and rash (6%).

The adverse reactions most commonly associated with SABRIL treatment discontinuation in ≥1% of IS patients were infections (1.5%), status epilepticus (1.2%), developmental coordination disorder (1.2%), dystonia (1.2%), hypotonia (1.2%), hypertonia (1.2%), weight increased (1.2%), and insomnia (1.2%).

Most Common Adverse Reactions in Controlled Clinical Trials

Infantile Spasms

In a randomized, placebo-controlled IS study with a 5 day double-blind treatment phase (n=40), the adverse events reported by >5% of SABRIL patients and that that occurred more frequently than in placebo patients were somnolence (SABRIL 45%, placebo 30%), bronchitis (SABRIL 30%, placebo 15%), ear infection (SABRIL 10%, placebo 5%), and otitis media acute (SABRIL 10%, placebo 0).

In a dose response study of low-dose (18-36 mg/kg/day) versus high-dose (100-148 mg/kg/day) vigabatrin, no clear correlation between dose and incidence of adverse events was observed. The treatment emergent adverse reactions (≥5% in either dose group) are summarized in Table 4.

Table 4. Treatment Emergent Adverse Events Occurring in ≥5% of Patients (Study 1A)

Body System Event	SABRIL Low Dose [N = 114] %	SABRIL High Dose [N = 108] %
Eye Disorders (other than field or acuity changes)		
Strabismus	5	5
Conjunctivitis	5	2
Gastrointestinal Disorders		
Vomiting	14	20
Constipation	14	12
Diarrhea	13	12
General Disorders		
Fever	29	19
Infections		
Upper respiratory tract infection	51	46
Otitis media	44	30
Viral infection	20	19
Pneumonia	13	11
Candidiasis	8	3
Ear infection	7	14
Gastroenteritis viral	6	5
Sinusitis	5	9
Urinary tract infection	5	6
Influenza	5	3
Croup infectious	5	1
Metabolism & Nutrition Disorders		
Decreased appetite	9	7
Nervous System Disorders		
Sedation	19	17
Somnolence	17	19
Status epilepticus	6	4
Lethargy	5	7
Convulsion	4	7
Hypotonia	4	6
Psychiatric Disorders		
Irritability	16	23
Insomnia	10	12
Respiratory Disorders		
Nasal congestion	13	4
Cough	3	8
Skin & Subcutaneous Tissue Disorders		
Rash	8	11

Refractory Complex Partial Seizures in Adults

Because controlled trials in infants were of short duration and enrolled few patients, the adverse events from clinical trials in adults are presented. Table 5 lists the treatment emergent adverse reactions that occurred in ≥2% of SABRIL patients and that occurred more frequently than in placebo patients from 2 U.S. add-on clinical studies of refractory complex partial seizures in adults.

Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
Eye Disorders		
Vision blurred	11	5
Diplopia	3	0
Eye disorder (other than field or acuity changes)	3	0
Asthenopia	2	0
Gastrointestinal Disorders		
Diarrhea	10	7
Nausea	9	8
Vomiting	7	6
Constipation	6	3
Abdominal pain upper	5	2
Dyspepsia	4	3
Stomach discomfort	3	1
Hemorrhoids	2	0
General Disorders		
Fatigue	27	16
Asthenia	5	2
Peripheral edema	5	1
Fever	5	3
Infections		
Nasopharyngitis	13	10
Upper respiratory tract infection	9	5
Influenza	5	4
Urinary tract infection	4	0
Injury		
Contusion	4	2
Metabolism and Nutritional Disorders		
Fluid retention	2	0
Increased appetite	2	0
Weight increased	8	3
Musculoskeletal Disorders		
Arthralgia	8	3
Back pain	6	2
Pain in extremity	5	4
Myalgia	3	2
Joint swelling	2	0
Muscle spasms	2	1
Shoulder pain	2	1
Nervous System Disorders		
Somnolence	22	13
Dizziness	21	17
Nystagmus	15	9
Tremor	14	8
Memory impairment	10	3
Coordination abnormal	9	2
Disturbance in attention	5	1
Sensory disturbance	5	2
Hyporeflexia	5	1
Parasthesia	5	1

Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
Lethargy	4	2
Hypoaesthesia	3	2
Sedation	2	0
Status epilepticus	2	0
Dysarthria	2	1
Psychiatric Disorders		
Irritability	10	7
Depression	7	3
Confusional state	6	1
Depressed mood	4	1
Anxiety	4	3
Thinking abnormal	3	0
Abnormal behavior	3	1
Aggression	2	0
Reproductive System		
Dysmenorrhea	7	3
Respiratory, and Thoracic Disorders		
Pharyngolaryngeal pain	9	5
Dyspnea	2	0
Sinus headache	4	1

6.2 Post Marketing Experience

The following serious adverse events have been reported since approval and use of SABRIL worldwide. All serious adverse events that are not listed above as adverse events reported in clinical trials, that are not relatively common in the population and are not too vague to be useful are listed in this section. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Events are categorized by system organ class.

Birth Defects: Congenital cardiac defects, congenital external ear anomaly, congenital hemangioma, congenital hydronephrosis, congenital male genital malformation, congenital oral malformation, congenital vesicoureteric reflux, dentofacial anomaly, dysmorphism, fetal anticonvulsant syndrome, hamartomas, hip dysplasia, limb malformation, limb reduction defect, low set ears, renal aplasia, retinitis pigmentosa, supernumerary nipple, talipes

Ear: Deafness

Endocrine: Delayed puberty

Gastrointestinal: Gastrointestinal hemorrhage, esophagitis

General: Developmental delay, facial edema, malignant hyperthermia, multi-organ failure

Hepatobiliary: Cholestasis

Nervous System: Dystonia, encephalopathy, hypertonia, hypotonia, muscle spasticity, myoclonus, optic neuritis

Psychiatric: Acute psychosis, apathy, delirium, hypomania, neonatal agitation, psychotic disorder

Respiratory: Laryngeal edema, pulmonary embolism, respiratory failure, stridor

Skin and Subcutaneous Tissue: Angioedema, maculo-papular rash, pruritus

7 DRUG INTERACTIONS

For detailed information about Drug Interactions see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions (12.3).

7.1 Phenytoin

A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies.

7.2 Other AEDs

There are no clinically significant pharmacokinetics interactions between SABRIL and either phenobarbital or sodium valproate. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

7.3 Clonazepam

In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

7.4 Oral Contraceptives

SABRIL is unlikely to affect the efficacy of steroid oral contraceptives.

7.5 Drug-Laboratory Test Interactions

SABRIL decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. In some patients, these enzymes become undetectable. The suppression of ALT and AST activity by SABRIL may preclude the use of these markers, especially ALT, to detect early hepatic injury.

SABRIL may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The following information is pertinent to the possible use of this dosage form in adults.

Pregnancy Category C. Vigabatrin produced developmental toxicity, including teratogenic and neurohistopathological effects, when administered to pregnant animals at clinically relevant doses. In addition, developmental neurotoxicity was observed in rats treated with vigabatrin during a period of postnatal development corresponding to the third trimester of human pregnancy. There are no adequate and well-controlled studies in pregnant women. SABRIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of vigabatrin (oral doses of 50 to 200 mg/kg) to pregnant rabbits throughout the period of organogenesis was associated with an increased incidence of malformations (cleft palate) and embryo-fetal death; these findings were observed in two separate studies. The no-effect dose for teratogenicity and embryolethality in rabbits (100 mg/kg) is approximately 1/2 the maximum recommended human dose (MRHD) of 3 g/day on a body surface area (mg/m^2) basis for adults treated for refractory complex partial seizures with vigabatrin. In rats, oral administration of vigabatrin (50, 100, or 150 mg/kg) throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal anatomic variations. The no-effect dose for embryo-fetal toxicity in rats (50 mg/kg) is approximately 1/5 the MRHD in adults on a mg/m^2 basis. Oral administration of vigabatrin (50, 100, 150 mg/kg) to rats from the latter part of pregnancy through weaning produced long-term neurohistopathological (hippocampal vacuolation) and neurobehavioral (convulsions) abnormalities in the offspring. A no-effect dose for developmental neurotoxicity in rats was not established; the low-effect dose (50 mg/kg) is approximately 1/5 the MRHD in adults on a mg/m^2 basis.

In a published study, vigabatrin (300 or 450 mg/kg) was administered by intraperitoneal injection to a mutant mouse strain on a single day during organogenesis (day 7, 8, 9, 10, 11, or 12). An increase in malformations (including cleft palate) was observed at both doses.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The early postnatal period in rats is

generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 those measured in pediatric patients receiving an oral dose of 50 mg/kg.

Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to SABRIL, physicians are advised to recommend that pregnant patients taking SABRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http:/www.aedpregnancyregistry.org.

8.2 Nursing Mothers

The following information is pertinent to the possible use of this dosage form in adults.

Vigabatrin is excreted in human milk. Because of the potential for serious adverse reactions from vigabatrin in nursing infants [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

SABRIL is indicated as monotherapy for pediatric patients with IS (1 month to 2 years of age) for whom the potential benefits outweigh the potential risk for developing permanent vision loss.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 21.5% in vigabatrin treated patients versus 4.1% in patients treated with other therapies. A dose-dependent relationship may exist, as children with IS who were exposed to a higher vigabatrin dose (≥125 mg/kg/day) had a prevalence of 29.5%, while those exposed to lower doses of vigabatrin had a prevalence of 12.5%; however, these differences were not statistically significant (p=0.099).

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment, although in a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)].

The specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with vigabatrin for refractory CPS. In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo patients.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 those measured in pediatric patients receiving an oral dose of 50 mg/kg.

8.4 Geriatric Use

The following information is pertinent to the possible use of this dosage form in adults.

Clinical studies of vigabatrin did not include sufficient numbers of patients aged 65 and over to determine whether they responded differently from younger patients.

Vigabatrin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Oral administration of a single dose of 1.5 g of vigabatrin to elderly (>65 years) patients with reduced creatinine clearance (<50 mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days. The renal clearance of vigabatrin was 36% lower in healthy elderly subjects (>65 years) than in young healthy males. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.5 Renal Impairment

Information about how to adjust the dose in pediatric patients with renal impairment is unavailable.

The following dose adjustments are pertinent to the possible use of this dosage form in adults with renal impairment:

In adults, dose adjustment, including initiating treatment with a lower dose, is necessary in patients with mild (creatinine clearance >50-80 mL/min), moderate (creatinine clearance >30-50 mL/min) and severe (creatinine clearance >10-30 mL/min) renal impairment [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Class

Vigabatrin is not a controlled substance.

9.2 Abuse

Vigabatrin did not produce adverse events or overt behaviors associated with abuse when administered to humans or animals. It is not possible to predict the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking behavior).

9.3 Dependence

Following chronic administration of vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, vigabatrin should be withdrawn gradually to minimize increased seizure frequency [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs), (5.6) and PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.5)].

10 OVERDOSAGE

10.1 Signs, Symptoms, and Laboratory Findings of Overdosage

Confirmed and/or suspected vigabatrin overdoses have been reported during clinical studies and in post marketing surveillance. No vigabatrin overdoses resulted in death. When reported, the vigabatrin dose ingested ranged from 3 g to 90 g, but most were between 7.5 g and 30 g. Nearly half the cases involved multiple drug ingestions including carbamazepine, barbiturates,

benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine.

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of vigabatrin overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, headache, hypotension, abnormal behavior, increased seizure activity, status epilepticus, and speech disorder. These symptoms resolved with supportive care.

10.2 Treatment or Management for Overdosage

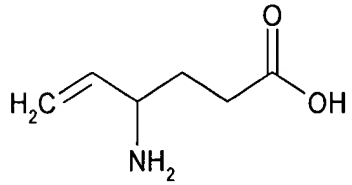
There is no specific antidote for SABRIL overdose. Standard measures to remove unabsorbed drug should be used, including elimination by emesis or gastric lavage. Supportive measures should be employed, including monitoring of vital signs and observation of the clinical status of the patients.

In an *in vitro* study, activated charcoal did not significantly adsorb vigabatrin.

The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

11 DESCRIPTION

Table 6. Description

Proprietary Name:	SABRIL®
Established Name:	Vigabatrin for Oral Solution
Dosage Form:	Packet
Route of Administration:	Oral
Pharmacologic Class of Drug:	Antiepileptic
Chemical Name:	(±) 4-amino-5-hexenoic acid
Structural Formula:	

SABRIL (vigabatrin) is available as a white granular powder for oral administration. Each packet contains 500 mg vigabatrin. Each packet also contains the inactive ingredient povidone. Vigabatrin is an oral antiepileptic drug with the chemical name (±) 4-amino-5-hexenoic acid. It is a racemate consisting of two enantiomers. The molecular formula is $C_6H_{11}NO_2$ and the molecular weight is 129.16.

Vigabatrin is a white to off-white powder which is freely soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n-octanol/water partition coefficient of vigabatrin is about 0.011 (log *P*=-1.96) at physiologic pH. Vigabatrin melts with decomposition in a 3-degree range within the temperature interval of 171°C to 176°C. The dissociation constants (pK_a) of vigabatrin are 4 and 9.7 at room temperature (25°C).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the central nervous system.

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

12.2 Pharmacodynamics

Effects on Electrocardiogram

There is no indication of a QT/QTc prolonging effect of SABRIL in single doses up to 6.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy adult subjects were administered a single oral dose of SABRIL (3 g and 6 g) and placebo. Peak concentrations for 6.0 g SABRIL were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

12.3 Pharmacokinetics

Vigabatrin displayed linear pharmacokinetics after administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g to 2.0 g twice daily. Bioequivalence has been established between the oral solution and tablet formulations.

Absorption
Following oral administration, vigabatrin is essentially completely absorbed. Time to maximum concentration (t_{max}) is approximately 2.5 hours in infants and about 1 hour in children following a single dose. There was little accumulation with multiple dosing. A food effect study involving administration of vigabatrin to healthy adult volunteers under fasting and fed conditions indicated that the C_{max} was decreased by 33%, t_{max} increased to 2 hours, and AUC was unchanged under fed conditions [see DOSAGE AND ADMINISTRATION, Infantile Spasms (2.1)].

Distribution
Vigabatrin does not bind to plasma proteins. Vigabatrin is widely distributed throughout the body; mean steady-state volume of distribution is 1.1 L/Kg (CV = 20%).

Metabolism and Elimination
Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. The half-life of vigabatrin in adults is about 7.5 hours and about 5.7 hours in infants. Following administration of $^{[14]}$C-vigabatrin to healthy adult male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

Pharmacokinetics in Special Populations

Geriatric
The renal clearance of vigabatrin in healthy elderly patients (≥65 years of age) was 36% less than those in healthy younger patients. A population PK analysis of patient data also confirmed these differences in age.

Pediatric
The clearance of infants and children were 2.4±0.8 and 5.7±2.5 L/h, respectively compared to 7 L/h in adults.

Gender
No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.

Race
No specific study was conducted to investigate the effects of race on SABRIL pharmacokinetics. A cross study comparison in adults between 23 Caucasian and 7 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that the AUC, C_{max}, and half-life were similar for the two populations. However, the mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4.0 L/hr). Inter-subject variability in renal clearance was 20% in Caucasians and was 30% in Japanese.

Renal Impairment

There is no information available about the pharmacokinetics of vigabatrin in pediatric patients with renal impairment.

In adult patients with mild renal impairment (CLcr from >50-80 mL/min), mean AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in comparison to the normal subjects. Mean AUC increased by two-fold and the terminal half-life increased by two-fold in patients with moderate renal impairment (CLcr from >30-50 mL/min) in comparison to the normal subjects. Mean AUC increased by 4.5-fold and the terminal half-life increased by 3.5-fold in patients with severe renal impairment (CLcr from >10-30 mL/min) in comparison to the normal subjects.

While dose adjustments are warranted in renally impaired pediatric patients, no data is available to guide dose adjustments in this patient population. Dosage adjustment in adults with renal impairment is recommended [see USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Hepatic Impairment
Vigabatrin is not significantly metabolized. The pharmacokinetics of vigabatrin in patients with impaired liver function have not been studied.

Drug Interactions

Phenytoin
A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies. *In vitro* drug metabolism studies indicate that decreased phenytoin concentrations upon addition of vigabatrin therapy are likely due to induction of cytochrome P450 2C enzymes in some patients. Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated.

Other AEDs
When co-administered with vigabatrin, phenobarbital concentration (from phenobarbital or primidone) was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be clinically relevant. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

Clonazepam
In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

Alcohol
Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g twice daily) indicated that neither drug influences the pharmacokinetics of the other.

Oral Contraceptives
In a double-blind, placebo-controlled study using a combination oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel, vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. Based on this study, vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives. Additionally, no significant difference in pharmacokinetic parameters (elimination half–life, AUC, C_{max}, apparent oral clearance, time to peak, and apparent volume of distribution) of vigabatrin were found after treatment with ethinyl estradiol and levonorgestrel.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Vigabatrin showed no carcinogenic potential in mouse or rat when given in the diet at doses up to 150 mg/kg/day for 18 months (mouse) or at doses up to 150 mg/kg/day for 2 years (rat). These doses are less than the maximum recommended human dose (MRHD) for IS (150 mg/kg/day) and for refractory complex partial seizures in adults (3 g/day) on a mg/m^2 basis.

Vigabatrin was negative in *in vitro* (Ames, CHO/HGPRT mammalian cell forward gene mutation, chromosomal aberration assay in rat lymphocytes) and in *in vivo* (mouse bone marrow micronucleus) assays.

No adverse effects on male or female fertility were observed in rats at oral doses up to 150 mg/kg/day (approximately 1/2 the MRHD of 3 g/day (on a mg/m^2 basis) for adults treated for refractory complex partial seizures with vigabatrin.

14 CLINICAL STUDIES

14.1 Infantile Spasms
The effectiveness of SABRIL as monotherapy was established for IS in two multicenter controlled studies. Both studies were similar in terms of disease characteristics and prior treatments of patients and all enrolled infants had a confirmed diagnosis of IS.

Study 1

Study 1 (N=221) was a multicenter, randomized, low-dose high-dose, parallel group, partially-blinded (caregivers knew the actual dose but not whether their child was classified as low or high dose; EEG reader was blinded but investigators were not blinded) study to evaluate the safety and efficacy of vigabatrin in patients <2 years of age with new-onset Infantile Spasms. Patients with both symptomatic and cryptogenic etiologies were studied. The study was comprised of two phases. The first phase was a 14 to 21 day partially-blind phase in which patients were randomized to receive either low- dose (18-36 mg/kg/day) or high-dose (100-148 mg/kg/day) vigabatrin. Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the patient became spasm-free on or before day 14, another 7 days of constant dose was administered. The primary efficacy endpoint of this study was the proportion of patients who were spasm-free for 7 consecutive days beginning within the first 14 days of vigabatrin therapy. Patients considered spasm-free were defined as those patients who remained free of spasms (evaluated according to caregiver response to direct questioning regarding spasm frequency) and who had no indication of spasms or hypsarrhythmia during 8 hours of CCTV EEG recording (including at least one sleep-wake-sleep cycle) performed within 3 days of the seventh day of spasm freedom and interpreted by a blinded EEG reader. Seventeen patients in the high dose group achieved spasm freedom compared with 8 patients in the low dose group. This difference was statistically significant (p=0.0375). Primary efficacy results are shown in Table 7.

Table 7. Spasm Freedom by Primary Criteria (Study 1A)

	SABRIL Treatment Group	
	18-36 mg/kg/day [N=114] n (%)	100-148 mg/kg/day [N=107] n (%)
Patients who Achieved Spasm Freedom	8 (7.0)	17 (15.9)

p=0.0375

Note: Primary criteria were evaluated based on caregiver assessment plus CCTV EEG confirmation within 3 days of the seventh day of spasm freedom.

Study 2

Study 2 (N=40) was a multicenter, randomized, double-blind, placebo-controlled, parallel group study consisting of a pre-treatment (baseline) period of 2-3 days, followed by a 5-day double-blind treatment phase during which patients were treated with vigabatrin (initial dose of 50 mg/kg/day with titration allowed to 150 mg/kg/day) or placebo. The primary efficacy endpoint in this study was the average percent change in daily spasm frequency, assessed during a pre-defined and consistent 2-hour window of evaluation, comparing baseline to the final 2 days of the 5-day double-blind treatment phase. No statistically significant differences were observed in the average frequency of spasms using the 2-hour evaluation window. However, a post-hoc alternative efficacy analysis, using a 24-

hour clinical evaluation window, found a statistically significant difference in the overall percentage of reductions in spasms between the vigabatrin group (68.9%) and the placebo group (17.0%) (p=0.030).

15 REFERENCES

None

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 SABRIL Packet

Each SABRIL packet contains 500 mg vigabatrin as a white to off-white granular powder.

NDC 67386-211-65: Packages of 50.

Store at 20-25°C (68-77°F). See USP controlled room temperature.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.5)

Caregivers must be informed of the availability of a Medication Guide. They must be instructed to read the Medication Guide prior to initiating treatment with SABRIL and with each prescription refill. Doctors must review the SABRIL Medication Guide with every caregiver prior to initiation of treatment. Caregivers should be instructed to administer SABRIL only as prescribed.

Physicians should confirm that caregiver(s) understand how to reconstitute SABRIL for Oral Solution and to administer the correct dose to their infants.

17.1 Vision Loss

Caregiver(s) should be informed of the risk of permanent vision loss, particularly loss of peripheral vision, from SABRIL, and the need for monitoring vision [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

Although vision testing in infants is insensitive, vision must be assessed to the extent possible at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy. Caregiver(s) should understand that vision testing is insensitive in infants and may not detect vision loss before it is severe. Caregiver(s) should also understand that if vision loss is documented, such loss is irreversible [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

Caregiver(s) should be informed that if changes in vision are suspected, they should notify their physician immediately.

17.2 MRI Abnormalities

Caregiver should be informed of the possibility of developing abnormal MRI signal changes of unknown clinical significance.

17.3 Suicidal Thinking and Behavior

The following information is pertinent to the possible use of this dosage form in adults.

Patients, their caregiver(s), and families should be counseled that AEDs, including SABRIL, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of concern should be reported immediately to healthcare providers [see WARNINGS AND PRECAUTIONS, Suicidal Behavior and Ideation (5.5)].

17.4 Use in Pregnancy

The following information is pertinent to the possible use of this dosage form in adults.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1), Nursing Mothers (8.2)].

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)]. Information on the registry can also be found at the website http:/www.aedpregnancyregistry.org.

17.5 Withdrawal of SABRIL Therapy

Caregiver(s) should be told not to suddenly discontinue SABRIL therapy in their infant. As with all AEDs, withdrawal should be gradual. In a controlled clinical study in patients with IS, vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days.

17.6 FDA-Approved Medication Guide

MEDICATION GUIDE

SABRIL® (*SAY-bril*)
(vigabatrin) Tablet

SABRIL® (*SAY-bril*)
(vigabatrin) for Oral Solution

Read the Medication Guide that comes with SABRIL before you or your baby starts taking SABRIL and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your or your baby's medical condition or treatment.

What is the most important information I should know about SABRIL?

SABRIL can cause serious side effects, including:

- **Permanent vision damage:**
  SABRIL can damage the vision of anyone who takes it. The most noticeable loss is in your ability to see to the side when you look straight ahead (peripheral vision). If this happens, it will not get better. People who take SABRIL do not lose all of their vision, but some people can have severe loss particularly to their peripheral vision. With severe vision loss you may only be able to see things straight in front of you (sometimes called 'tunnel vision'). You may also have blurry vision.

- **Vision loss and use of SABRIL in adults:** Because of the risk of vision loss, SABRIL is used to treat complex partial seizures (CPS) only in people who do not respond well enough to several other medicines.

Tell your doctor right away if you:

- think you are not seeing as well as before you started taking SABRIL
- start to trip, bump into things, or are more clumsy than usual
- are surprised by people or things coming in front of you that seem to come out of nowhere

These changes can mean that you have damage to your vision. Your doctor will test your visual fields (including peripheral vision) and visual acuity (ability to read an eye chart) before you start SABRIL or within 4 weeks after starting SABRIL, and at least every 3 months after that until SABRIL is stopped. Even if your vision seems fine, it is important that you get these regular vision tests because damage can happen to your vision before you notice any changes. These vision tests cannot prevent the vision damage that can happen with SABRIL, but they do allow you to stop SABRIL if vision has gotten worse, which usually will lessen further damage. If you do not have these vision tests regularly, your doctor may stop prescribing SABRIL for you. You should also have a vision test after SABRIL is stopped.

If you drive and your vision is damaged by SABRIL, driving might be more dangerous, or you may not be able to drive safely at all. You should discuss this with your doctor.

- **Vision loss in babies:** Because of the risk of vision loss, SABRIL is used in babies (1 month to 2 years old) with infantile spasms (IS) only when you and your doctor decide that the possible benefits of SABRIL are more important than the risks. Parents or caregivers are not likely to recognize the symptoms of vision loss in babies until it is severe. Doctors may not find vision loss in babies until it is severe. It is difficult to test vision in babies, but all

babies should have a vision test before starting SABRIL or within 4 weeks after starting SABRIL, and every 3 months after that until SABRIL is stopped. You should have a vision test for your baby after SABRIL is stopped.

Tell your doctor right away if you think that your baby is:

- not seeing as well as before taking SABRIL
- acting differently than normal

Even if your baby's vision seems fine, it is important to get regular vision tests because damage can happen before your baby acts differently. Even these regular vision exams may not show the damage to your baby's vision before it is serious and permanent. If your baby does not have these vision tests regularly, your doctor may stop prescribing SABRIL for your baby. If your baby is not able to complete vision testing, your doctor may continue prescribing SABRIL for your baby. But, your doctor will not be able to watch for vision loss in your baby.

In all people who take SABRIL:

- You are at risk for vision loss with any amount of SABRIL
- Your risk of vision loss may be higher the more SABRIL you take daily and the longer you take it
- It is not possible for your doctor to know when vision loss will happen. It could happen soon after starting SABRIL or any time during treatment. It may even happen after treatment has stopped.

Because Sabril might cause vision loss, it is available to doctors and patients only under a special program called SHARE. As part of the SHARE program, among other things, your doctor will have to test your or your baby's vision frequently while you or your baby are being treated with Sabril, and even after you or your baby stops treatment. You also have to agree to be in the SHARE program, and agree to have your or your baby's vision tested regularly. Your doctor will explain the details of the SHARE program to you.

MRI changes. Brain pictures taken by magnetic resonance imaging (MRI) show changes in some babies after they are given SABRIL. It is not known if these changes are harmful.

Risk of suicidal thoughts or actions. Like other antiepileptic drugs, SABRIL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it. Call a doctor right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability

- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your doctor as scheduled.
- Call your doctor between visits as needed, especially if you are worried about symptoms.

Do not stop SABRIL without first talking to a healthcare provider.

- Stopping SABRIL suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures.

SABRIL can be prescribed only to people who are enrolled in a program called SHARE. Before you or your baby can begin taking SABRIL, you must read and agree to all of the instructions in the SHARE program.

What is SABRIL?

SABRIL Tablets is a prescription medicine used along with other treatments to treat adults with CPS if:

- The CPS does not respond well enough to several other treatments, and
- You and your doctor decide the possible benefit of taking SABRIL is more important than the risk of vision loss.

SABRIL should not be the first medicine used to treat your CPS.

SABRIL for Oral Solution is a prescription medicine used to treat babies, one month to two years old who have IS, if you and your doctor decide the possible benefits of taking SABRIL are more important than the possible risk of vision loss.

If you are an adult with CPS, you must sign an agreement form before you can receive SABRIL.

If you are the parent or caregiver of a baby with IS, you must sign an agreement form before your baby can receive SABRIL.

What should I tell my doctor before starting SABRIL?

If you are an adult with CPS, before taking SABRIL tell your doctor if you have or had:

- depression, mood problems or suicidal thoughts or behavior
- an allergic reaction to SABRIL, such as hives, itching, or trouble breathing

- any vision problems
- any kidney problems
- low red blood cell counts (anemia)
- any nervous or mental illnesses, such as depression, thoughts of suicide, or attempts at suicide
- any other medical conditions
- are breastfeeding or planning to breastfeed. SABRIL can pass into breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take SABRIL.
- are pregnant or plan to become pregnant. It is not known if SABRIL will harm your unborn baby. You and your healthcare provider will have to decide if you should take SABRIL while you are pregnant.

Pregnancy Registry:

If you become pregnant while taking SABRIL, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy.

Before giving SABRIL to your baby, tell the doctor about all of your baby's medical conditions, including if your baby has or ever had:

- an allergic reaction to SABRIL, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems

Tell your doctor about all the medicines you or your baby take, including prescription and non-prescription medicines, vitamins, and herbal supplements. SABRIL and other medicines may affect each other causing side effects.

How should I take SABRIL?

If you are an adult with CPS:

- Your doctor will explain the SHARE Program to you
- You will receive SABRIL from a specialty pharmacy
- Take SABRIL tablets exactly as prescribed by your doctor. SABRIL tablets are usually taken two times each day.
- You may take SABRIL tablets with or without food
- Before you start taking SABRIL, talk to your doctor about what you should do if you miss a dose of SABRIL
- **Do not stop taking SABRIL suddenly.** This can cause serious problems. Stopping SABRIL or any seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures. You should follow your doctor's instructions on how to stop taking SABRIL.
- Tell your doctor right away about any increase in seizures while you are stopping SABRIL

- If SABRIL does not improve your seizures enough within 3 months, your doctor will stop prescribing SABRIL for you
- **Do not stop taking SABRIL without talking to your doctor.** If SABRIL improves your seizures, you and your doctor should talk about whether the benefit of taking SABRIL is more important than the risk of vision loss, and decide if you will continue to take SABRIL.

If you are giving SABRIL to your baby for IS:

- Your doctor will explain the SHARE program to you
- You will receive SABRIL for oral solution from a specialty pharmacy
- Mix SABRIL for oral solution and give it to your baby exactly as prescribed by your doctor. Do not stop giving SABRIL for oral solution to your baby unless your doctor tells you to.
- SABRIL for oral solution is usually given two times each day
- SABRIL for oral solution can be given to your baby at the same time as their food, but the powder should not be mixed with their food. SABRIL for oral solution powder should be mixed with water only.
- See the end of this Medication Guide for detailed instructions for how to mix SABRIL for oral solution and give the medicine to your baby
- Before your baby starts taking SABRIL, speak to your baby's doctor about what to do if your baby misses a dose, vomits, spits up, or only takes part of the dose of SABRIL
- **Stopping SABRIL suddenly can cause serious problems**. Stopping SABRIL or any seizure medicine suddenly can cause seizures that will not stop. You should follow your doctor's instructions on how to stop giving SABRIL to your baby. SABRIL does not work in all babies. If your baby's seizures do not improve enough within 2 to 4 weeks, the doctor will stop SABRIL.
- **Tell your doctor right away about any increase in your baby's seizures while stopping SABRIL**

What should I avoid while taking SABRIL?

SABRIL causes sleepiness and tiredness. Adults taking SABRIL should not drive, operate machinery, or perform any hazardous task, unless you and your doctor have decided that you can do these things safely.

What are the possible side effects of SABRIL?

SABRIL can cause serious side effects. See "What is the most important information I should know about SABRIL?"

These other serious side effects happen in **adults**. It is not known if these side effects also happen in babies who take SABRIL.

- Low red blood cell counts (anemia)
- Sleepiness and tiredness. See "What should I avoid while taking SABRIL?"
- Nerve problems. Symptoms of a nerve problem can include numbness and tingling in your toes or feet. It is not known if nerve problems will go away after you stop taking SABRIL.
- Weight gain that happens without swelling
- Swelling

If you are an adult with CPS, SABRIL may make certain types of seizures worse. Tell your doctor right away if your seizures get worse.

The most common side effects of SABRIL in adults include:

- problems walking or feel uncoordinated
- feel dizzy
- shaking (tremor)
- joint pain
- memory problems and not thinking clearly
- eye problems: blurry vision, double vision and eye movements that you cannot control

If you are giving SABRIL to your baby for IS

SABRIL may make certain types of seizures worse. You should tell your baby's doctor right away if your baby's seizures get worse. Tell your baby's doctor if you see any changes in your baby's behavior.

The most common side effects of SABRIL in **babies and young children** include:

- sleepiness - SABRIL may cause your baby to be sleepy. Sleepy babies may have a harder time suckling and feeding, or may be irritable.
- ear infection
- irritability

Tell your doctor if you or your baby have any side effect that bother you or that does not go away. These are not all the possible side effects of SABRIL. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SABRIL?

Store SABRIL tablets and SABRIL packets at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep SABRIL tablets and SABRIL powder in the container they come in.

Keep SABRIL and all medicines out of the reach of children.

General information about SABRIL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SABRIL for a condition for which it was not prescribed. Do not give SABRIL to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SABRIL. If you would like more information about SABRIL, talk with your doctor. You can ask your pharmacist or

doctor for information about SABRIL that is written for health professionals. For more information, go to **www.SABRIL.net or call 1-800-455-1141.**

What are the ingredients in SABRIL?

Active Ingredient: vigabatrin

Inactive Ingredients in **SABRIL tablets**: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide.

Inactive Ingredient in **SABRIL powder**: povidone.

Instructions for mixing and giving SABRIL for oral solution to your baby

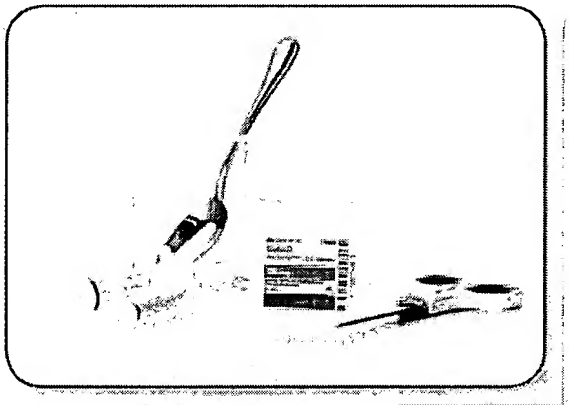
Sabril®
vigabatrin
500 mg tablet
500 mg powder for oral solution

Be sure to read, understand, and follow these instructions for the right way to mix SABRIL for oral solution to give to your baby. Talk to your doctor if you have any questions about the right dose of medicine to give your baby or how to mix it.

- SABRIL for oral solution comes as a powder
- Each packet contains 500 mg of SABRIL for oral solution
- The powder in the packets must be mixed with **water only.** The water may be cold or at room temperature
- Your baby's doctor will tell you:
  - how many packets of SABRIL for oral solution your baby will need for each dose
  - how many milliliters (mLs) of water to use to mix a dose of SABRIL for oral solution for your baby
  - how many milliliters (mLs) of the mixture you will need to give to your baby after the powder is mixed with water. This is the amount of medicine to give your baby for one dose of SABRIL for oral solution
- SABRIL for oral solution should be given to your baby right away after it is mixed

Supplies needed to mix a dose of SABRIL for oral solution:

- The number of packets of SABRIL for oral solution needed for your baby's dose
- 2 clean cups: 1 for mixing and 1 for water. The cup used for mixing SABRIL for oral solution should be clear so you can see if the powder is dissolved
- Water to mix with the SABRIL for oral solution
- Small 3 mL oral syringe and large 10 mL oral syringe provided
- Small spoon or other clean utensil to stir with
- Scissors



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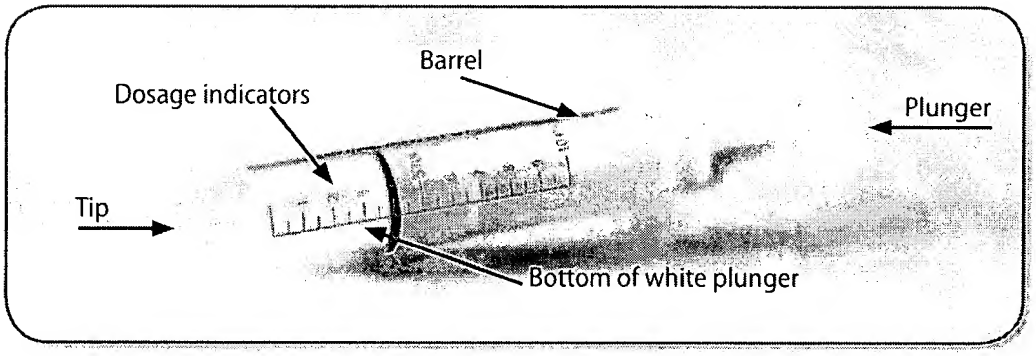
Oral syringe detail



1. Get **1** of the empty cups and the number of packets you will need for 1 dose.

2. Before you open the packet, tap it to settle all the powder at the bottom of the packet.

3. Use a pair of scissors to cut open the SABRIL for oral solution packet along the dotted line.

4. Empty the entire contents of the SABRIL for oral solution packet into **1** of the clean empty cups (Figure A).

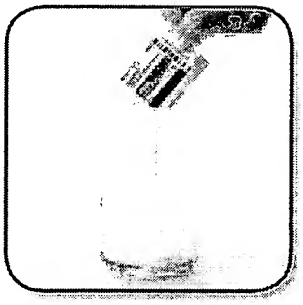


Figure A

5. Repeat steps 2 through 4 above to open all of the packets needed for 1 dose of SABRIL for oral solution.

6. Get the **other** cup and fill it half way with water (Figure B). Do not mix SABRIL for oral solution with anything other than water.

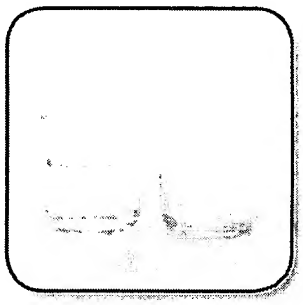


Figure B

7. You will use the larger oral syringe (10 mL) to draw up the water needed to mix with the powder from the packets. **Each packet of SABRIL for oral solution needs to be mixed with 10 mL of water.**

   For example:

   - If you are using 1 packet of SABRIL for oral solution, you will need to use 10 mL of water (fill the 10 mL oral syringe 1 time)
   - If you are using 2 packets of SABRIL for oral solution, you will need to use 20 mL of water (fill the 10 mL oral syringe 2 times)
   - If you are using 3 packets of SABRIL for oral solution, you will need to use 30 mL of water (fill the 10 mL oral syringe 3 times)

8. Get the **larger** oral syringe (the 10 mL oral syringe). Use the oral syringe to draw up 10 mL of water. To do this, put the **tip** of the oral syringe all the way into the water in your cup. Then pull the plunger up towards you until the black ring of the white plunger is at the 10 mL line on the barrel of the oral syringe (Figure C).

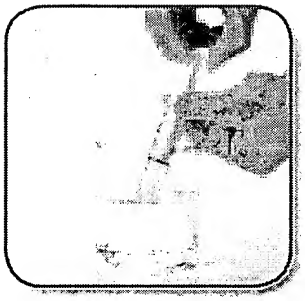


Figure C

9. If you see bubbles of air in the oral syringe after drawing up the water, turn the oral syringe so the tip is pointing up (Figure D). The air will move to the top of the oral syringe. Pull the plunger back towards you and then push it back gently into the oral syringe to get rid of the bubbles. Tiny bubbles are normal.

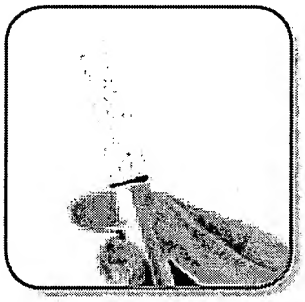


Figure D

10. Make sure the oral syringe is full of water up to the 10 mL line (Figure E).

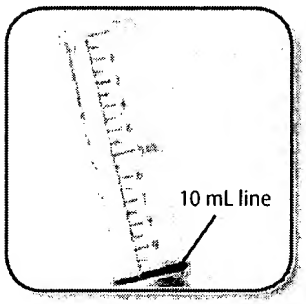


Figure E

11. Empty the water from the oral syringe directly into the cup with the SABRIL for oral solution. This is done by pushing the plunger of the oral syringe down **slowly** while the tip of the oral syringe is in the cup (Figure F).

Repeat steps 8 through 11 until all of the water that is needed to mix 1 dose of SABRIL for oral solution has been added to the cup containing the powder.

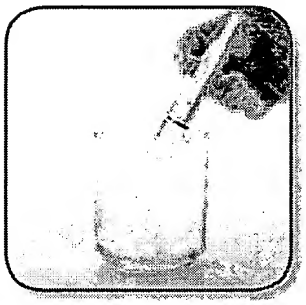


Figure F

12. Stir the mixture with the small spoon or other clean utensil until the solution is clear (Figure G). This means that all of the powder is dissolved.

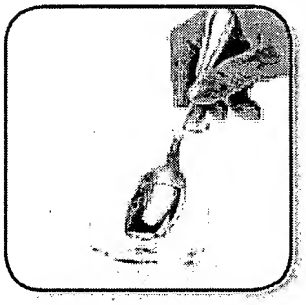


Figure G

13. Use the oral syringe to draw up the number of mLs of the mixture told to you by your doctor. If you are giving **3 mL or less** of the mixture, use the smaller oral syringe (3 mL oral syringe). If you are giving **more than 3 mL** of the mixture, use the 10 mL oral syringe. (This is the oral syringe that you just used to add the water.)

14. Put the **tip** of the oral syringe all the way into the mixture. Pull the plunger up towards you to draw up the mixture. Stop when the black ring of the white plunger lines up with the marking on the barrel of the oral syringe that matches the number of mLs of mixture your doctor told you to give your baby (Figure H).

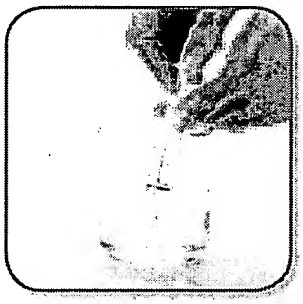


Figure H

15. If you see bubbles or air in the oral syringe after drawing up the mixture, turn the oral syringe so the tip is pointing up (Figure I). The air will move to the top of the oral syringe. Pull the plunger back towards you and then gently push it back in the oral syringe in order to get rid of the bubbles. Tiny bubbles are normal.

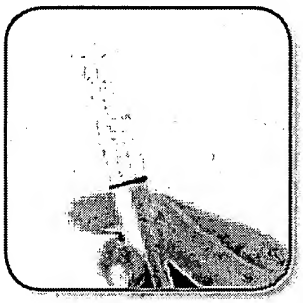


Figure I

16. Place the tip of the oral syringe into your baby's mouth and point the oral syringe towards either of the baby's cheeks (Figure J). Push on the plunger slowly, **a small amount at a time,** until all of the mixture in the oral syringe is given.

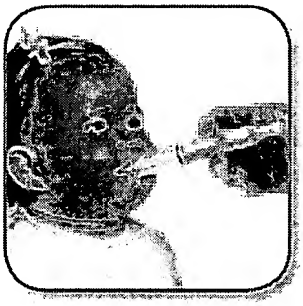


Figure J

17. If the dose you are giving your baby is larger than 10 mL, repeat steps 14 through 16 until you give the total dose of mixture prescribed by the doctor.

18. Throw away any mixture that is left over. Do not save and reuse leftover mixture.

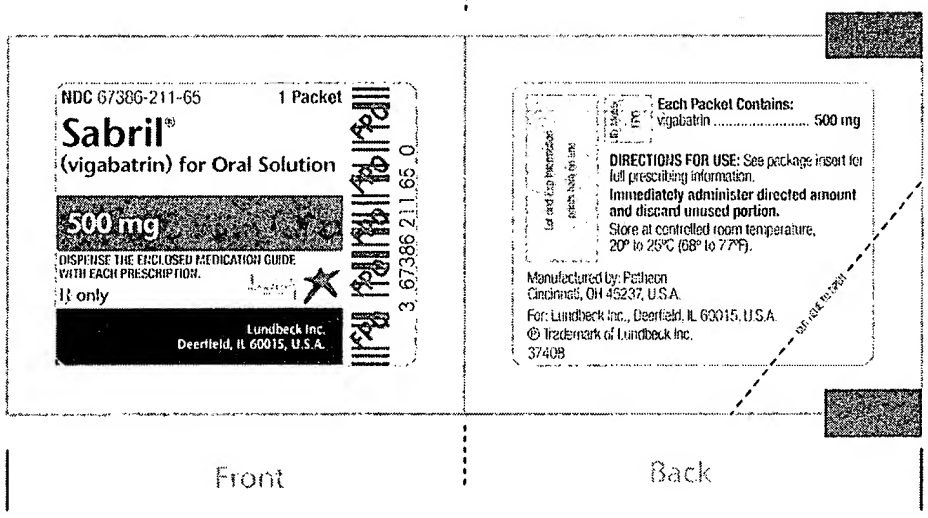
19. Wash the oral syringes and mixing cups in warm water. To clean the oral syringes, remove the plunger by gently pulling it straight out of the barrel. The barrel and plunger can be hand washed with soap and water, rinsed, and allowed to dry, or the barrel and plunger can be placed in a dishwasher utensil rack, machine washed, and dried.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Marketed by:
Insert Lundbeck Inc. logo
Lundbeck Inc.
Deerfield, IL 60015, U.S.A.

Insert Lundbeck Inc. logo

Issued August 2009


NDC 67386-211-65
1 Packet
Sabril®
(vigabatrin) for Oral Solution
500 mg
DISPENSE THE ENCLOSED MEDICATION GUIDE WITH EACH PRESCRIPTION.
℞ only
Lundbeck Inc.
Deerfield, IL 60015, U.S.A.
3 67386 211 65 0
Each Packet Contains:
vigabatrin ..... 500 mg
DIRECTIONS FOR USE: See package insert for full prescribing information.
Immediately administer directed amount and discard unused portion.
Store at controlled room temperature, 20° to 25°C (68° to 77°F).
Manufactured by: Patheon
Cincinnati, OH 45237, U.S.A.
For: Lundbeck Inc., Deerfield, IL 60015, U.S.A.
® Trademark of Lundbeck Inc.
37408

Front

Back

Sabril® (vigabatrin) for Oral Solution

NDC 67386-211-65

50 Packets

Each Packet Contains:

vigabatrin ..... 500 mg

DIRECTIONS FOR USE:

See package insert for full prescribing information.
Immediately administer directed amount and discard unused portion.

Store at controlled room temperature, 20° to 25°C (68° to 77°F).

Manufactured by: Patheon, Cincinnati, OH 45237 U.S.A.
For: Lundbeck Inc., Deerfield, IL 60015, U.S.A.

® Trademark of Lundbeck Inc.

37088

NDC 67386-211-65

50 Packets

Sabril® (vigaba

DISPENSE THE ENCLOSED MEDICATIC

℞ only

Lundbeck Inc.
Deerfield, IL 60015, U.S.A.

APPENDIX A

RISK EVALUATION & MITIGATION STRATEGY (REMS)

Title:	Risk Evaluation & Mitigation Strategy (REMS): Support, Help and Resources for Epilepsy (SHARE)
Product Name:	Sabril (vigabatrin) NDAs 20-427, 22-006
Sponsor:	Lundbeck Inc. Four Parkway North Deerfield, Illinois 60015 Jenny Swalec, Sr. Director, Global Regulatory Affairs 847-282-1066
Date:	21 August 2009

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

The goals of the REMS are:

1) To reduce the risk of a Sabril-induced vision loss while delivering benefit to the appropriate patient populations;

2) To ensure that all patients receive a baseline ophthalmologic evaluation; 50% of patients will receive within 2 weeks of starting Sabril and 100% within 4 weeks;

3) To discontinue Sabril therapy in patients who experience an inadequate clinical response;

4) To detect Sabril-induced vision loss as early as possible;

5) To ensure regular vision monitoring to facilitate ongoing benefit-risk assessments; and

6) To inform patients/parent or legal guardian of the serious risks associated with Sabril, including vision loss and increased risk of suicidal thoughts and behavior.

II. REMS ELEMENTS

A. Medication Guide

Lundbeck will ensure that a Medication Guide is dispensed with each prescription of Sabril and in accordance with 21CFR 208.24. The Medication Guide will be included in the Sabril Starter Kit to be reviewed with the patient/parent or legal guardian by the physician prior to starting the patient on Sabril therapy.

Please see appended Medication Guide.

B. Communication Plan

At product launch (that is, during the first 6 months after product approval) and yearly for 3 years thereafter Lundbeck will send a Dear Healthcare Professional Letter via direct mail to all registered ophthalmologists. The Sabril package insert will accompany the letter. Additionally, Lundbeck Inc. field representatives will call on neuro-ophthalmologists and/or ophthalmologists at key epilepsy centers at product launch to disseminate the Sabril package inserts.

The Dear Healthcare Professional Letter is part of the REMS and is appended.

C. Elements To Assure Safe Use

1) Healthcare providers who prescribe Sabril will be specially certified under 505-1 (f)(3)(A).
   a) Lundbeck Inc. will ensure that prescribers enrolled in the REMS program are specially certified. Lundbeck Inc. will ensure that, to become certified, prescribers attest to their understanding of the REMS program requirements and the risks associated with Sabril, and that prescribers commit to the following:
      i) Reading the full prescribing information (PI) and Medication Guide;
      ii) Having knowledge of the approved indications for Sabril;
      iii) Having experience in treating epilepsy;
      iv) Having knowledge of the risks of Sabril, especially vision loss;
      v) If prescribing for infantile spasms, having knowledge of the risk of MRI abnormalities with use of Sabril;
      vi) Assessing the effectiveness of Sabril within 2-4 weeks in infants and within 12 weeks in adults; in the case that insufficient clinical benefit has occurred, Sabril will be discontinued; for patients discontinuing Sabril at this evaluation, a Treatment Maintenance Form will not be completed; for patients continuing

treatment, a Treatment Maintenance Form will be completed and faxed to the REMS coordinating center;

vii) Ordering and reviewing visual assessment at the time of initiation of Sabril using the Ophthalmologic Assessment Form (with the baseline assessment to be conducted within 4 weeks of starting Sabril), and every 3 months after initiating Sabril therapy; the Ophthalmologic Assessment Form will be faxed to the REMS coordinating center;

viii) Educating patients on the risks and benefits of Sabril;

ix) Enrolling all patients who take Sabril in the REMS program by completing and submitting the Treatment Initiation Form and the Patient/Parent/Legal Guardian-Physician Agreement Form;

x) Reviewing the Sabril Medication Guide with every patient;

xi) Counseling the patient if the patient is not complying with the required vision monitoring beyond the baseline test, and removing the patient from therapy if the patient still fails to comply with required vision monitoring;

(1) Should discontinuation be required, discontinuation will be accomplished by tapering the patient from therapy as described in the therapy by tapering the patient from therapy as described in the Dear HCP Medication Taper Letter; and

xii) Reporting to the Sponsor at 1-800-455-1141 any serious adverse events with Sabril and providing all known details of the event.

b) The prescriber may exempt certain patients from vision assessment, using the Ophthalmologic Assessment form, if:

i) The patient is blind

ii) The patient's general neurological condition precludes the need for visual assessment

iii) The patient's medical condition prevents visual assessment being performed safely, documented by the prescriber.

iv) For other reasons documented by the prescriber.

c) The following materials are part of the REMS and are appended

(1) Dear Healthcare Professional (HCP) Letter

(2) Dear HCP Medication Taper Letter

(3) Prescriber Enrollment and Agreement Form

(4) Treatment Initiation Form

(5) Treatment Maintenance Form

(6) Ophthalmologic Assessment Form

(7) Patient-Physician Agreement- Refractory CPS

(8) Parent/Legal Guardian –Physician Agreement-IS

Lundbeck Inc. will maintain a database of certified prescribers in the REMS program. Lundbeck Inc. will ensure that prescribers comply with the requirements of the REMS and may de-enroll noncompliant prescribers.

2) Pharmacies that dispense Sabril will be specially certified by Lundbeck Inc, under 505-1(f)(3)(B).

Lundbeck Inc. will ensure that to be certified, each pharmacy does the following; pharmacies not complying may be de-enrolled by Lundbeck Inc:

a) designates a representative who is trained on the REMS program

b) dispenses Sabril only to patients who are enrolled in the REMS program, and whose continued eligibility has been established within the REMS

c) obtains treatment forms and prescriptions only from the REMS coordinating center.

d) obtains a dispensing authorization from the REMS coordinating center before dispensing the first Sabril prescription and before dispensing each refill.

e) trains pharmacy staff on the REMS program procedures and REMS materials for dispensing

f) agrees that the certified pharmacy may be audited by the FDA, Lundbeck Inc, or a third party designated by Lundbeck Inc.

3) Sabril will be dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D):

a) Lundbeck Inc. will ensure that each patient treated with Sabril is enrolled in the Sabril REMS before Sabril is dispensed to him or her. Lundbeck Inc. will ensure that, to become enrolled, each patient or parent/legal guardian must sign a Patient/Parent/Legal Guardian-Physician Agreement Form indicating that:

i) they have read the Medication Guide;

ii) the prescriber has explained the risk of visual loss;

iii) vision loss, should it occur, is irreversible;

iv) that prescribed vision assessments must be obtained;

v) periodic vision assessment, although it does not protect against all vision loss, is required for the duration of therapy, and after stopping Sabril; and

vi) response to Sabril will be assessed after a short trial period (3 months for complex partial seizures and 1 month for infantile spasms); should the patient's response to Sabril be insufficient, therapy with Sabril will be stopped

b) The following materials are part of the REMS and are appended

(1) Patient-Physician Agreement- Refractory CPS

(2) Parent/Legal Guardian –Physician Agreement-IS

(3) Treatment Maintenance Form

(4) Ophthalmologic Assessment Form

4) Each patient using the drug will be enrolled in a registry under 505-1(f)(3)(F) The registry will collect prescriber specialty, patient demographics, diagnosis, prior and concurrent anti-seizure medications, periodic ophthalmologic assessment data (i.e., the results of every 3-month monitoring), and the proportion of patients receiving Sabril for refractory complex partial seizures and infantile spasms who respond/do not respond to Sabril during the treatment initiation phase.

D. Implementation System

The Implementation System will include the following. Lundbeck Inc. will:

1) maintain a validated and secured (21 CFR Part 11 compliant) database of certified pharmacies, certified prescribers and enrolled patients.

2) monitor distribution data to ensure that only certified pharmacies are distributing and dispensing Sabril.

3) train all personnel working for the REMS coordinating center (TheraCom) directly responsible for the Sabril REMS program and site managers at all certified pharmacies. Lundbeck Inc. will audit all certified pharmacies and the REMS coordinating center on an annual basis.

4) ensure that the REMS coordinating center receives each enrolled patient's completed Treatment Maintenance Form documenting an assessment of risk-benefit prior to authorizing the maintenance phase of therapy.

5) ensure that the REMS coordinating center obtains the completed Ophthalmologic Assessment Form for all registered patients at 3-month intervals (plus a 90-day grace period, as detailed in the REMS Supporting Document) prior to authorizing continued dispensing of refills

6) ensure that certified pharmacies dispense Sabril only if they receive authorization for each dispensing from the REMS coordinating center.

7) ensure that patients who do not comply with the vision monitoring requirements of the REMS are tapered from Sabril.

8) monitor and evaluate the implementation of the elements provided for under Sections C1, C.2, C.3, and C.4, above, in the manner described in the REMS supporting document, and take reasonable steps to work to improve implementation of these elements.

E. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA every 6 months from the date of approval of the REMS for 1 year, and then annually thereafter. The assessment period will close no earlier than 60 days prior to the date the respective assessment is due. The assessment is to be received by the FDA on the due date.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

Lundbeck Inc. is writing to inform you of the approval of SABRIL® (vigabatrin), pronounced say-bril, by the Food and Drug Administration (FDA) for the following indications: As adjunctive therapy in adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments and as monotherapy for pediatric patients with infantile spasms (IS).

Decisions to use SABRIL to treat refractory CPS and IS must balance the potential benefits with the risks of therapy.

SABRIL causes irreversible bilateral concentric constriction of the visual field in 30 percent or more of adult patients, and, therefore, has a Risk Evaluation and Mitigation Strategy (REMS) associated with its use. Information on how patients and physicians can gain access to SABRIL and guidance on how to evaluate SABRIL-induced vision loss can be found through the SHARE Program which is discussed at the end of this letter.

Copies of the full Prescribing Information and Medication Guide are enclosed for your reference. Two specific effects of SABRIL are highlighted below:

Vision Loss
SABRIL causes permanent bilateral concentric constriction of the visual field in 30 percent or more of adult patients. Vision loss can range in severity from mild to severe, including tunnel vision to within about 10 degrees of visual fixation and can result in disability. In some cases, SABRIL can also damage the central retina and may decrease visual acuity. The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years, although the risk of vision loss may increase with increasing duration of exposure. There is no dose known to be free of risk of vision loss, although the risk of vision loss may increase with increasing dose and cumulative exposure. The possibility that vision loss can worsen despite discontinuation of SABRIL has not been excluded.

Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe; therefore, appropriate vision monitoring is needed for detection. Monitoring of vision by an ophthalmic professional (defined as having expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina) is required.

Vision monitoring is mandatory in adults receiving SABRIL for refractory CPS at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.

Assessing vision loss is difficult in children and therefore the frequency and extent of vision loss in infants and children is poorly characterized. Vision monitoring is required to the extent possible in infants receiving SABRIL at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. This assessment should include visual acuity and visual field whenever possible. The appropriate diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor periodically must be documented under the SHARE program. In those patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate caregiver counseling, and

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

with documentation in the SHARE program of the inability to test vision. Results from ophthalmic monitoring must be interpreted with caution, as reliability and predictive value are variable

Please read the full Prescribing Information for additional details.

Magnetic Resonance Imaging (MRI) Abnormalities

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated with SABRIL. The potential for long-term clinical sequelae and the need for monitoring have not been adequately studied. In animals that received vigabatrin, similar MRI abnormalities were correlated histologically with microvacuoles, consistent with a process of intramyelinic edema in those animals. Vacuolar changes considered distinct from intramyelinic edema, as well as other neurotoxicity and neurobehavioral abnormalities have also been observed in animals.

Brain MRI abnormalities, attributable to SABRIL have not been observed in adult or older pediatric patients treated with SABRIL for CPS.

Please read the full Prescribing Information for additional details.

S.H.A.R.E Program

To support patients and prescribers in their evaluation of the benefits and risks of SABRIL and their decision to initiate therapy, and to support the evaluators of SABRIL induced vision loss, Lundbeck Inc. has established the SHARE program which stands for Support, Help and Resources for Epilepsy. SHARE administers the SABRIL Risk Evaluation & Mitigation Strategy (REMS) program and the associated distribution and reimbursement services. All physicians who prescribe SABRIL and all patients who take SABRIL must be registered in the SHARE program. Ophthalmologists do not need to be registered.

Please visit the Lundbeck SHARE website at www.lundbeckshare.com or call SHARE at 1-888-45-SHARE for registration information. Medical inquiries should be directed to the Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Patient Safety Department at 1-800-455-1141.

Sincerely,

Lundbeck Inc.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

Based on our conversation with you on *(insert date),* you indicated that you wish to continue treating patient, *(insert name)* with SABRIL after their completed Evaluation Phase of SABRIL therapy. We are writing to inform you that since we have not received a Treatment Maintenance Form for your patient, *(insert name)* which is mandatory for continued treatment with SABRIL, your next prescription must be written to taper *(insert name)* off of SABRIL, as no additional refills will be provided following completion of the taper.

This letter serves to remind you of the potential issues surrounding the abrupt withdrawal of SABRIL and provides the medication tapering recommendations from the Withdrawal of SABRIL Therapy Section of the approved labeling.

- SABRIL should not be discontinued abruptly and suddenly.
- As with all antiepileptic drugs, SABRIL should be withdrawn gradually to minimize increased seizure frequency.

An example of a tapering schedule employed in controlled clinical studies in adults with complex partial seizures is as follows: Vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued. For example, if a patient was taking 3 g/day, the taper schedule was:

- Week 1: 2 g/day = two tablets twice per day = 28 tablets total
- Week 2: 1 g/day = one tablet twice per day = 14 tablets total
- Week 3: Sabril completely discontinued

This example tapering schedule would require a total of 42 tablets of SABRIL.

An example of a tapering schedule employed in a controlled clinical study in patients with infantile spasms is as follows: Vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days. For example if a patient was taking 150 mg/kg/day (75 mg/kg BID), the taper schedule was:

- Days 1-3: 100 mg/kg/day (50 mg/kg BID)
- Days 4-6: 50 mg/kg/day (25 mg/kg BID)
- Days 7-10: 25 mg/kg/day (12.5 mg/kg BID)
- Day 11: Vigabatrin completely discontinued.

Read the full Prescribing Information in the approved labeling for additional details.

Please call the SHARE call center at 1-888-45-SHARE with any questions, concerns, or updates regarding this patient.

Other medical inquiries should be directed to the Lundbeck Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Lundbeck Patient Safety Department at 1-800-455-1141.

Sincerely,

Lundbeck Inc.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

We are writing to inform you that we have not received documentation that your patient, *(insert name)*, has obtained vision monitoring that is required in order to continue receiving SABRIL (vigabatrin). According to the Risk Management and Evaluation Strategy (REMS) program requirements, this patient will need to be tapered off of SABRIL.

Unless verification of vision monitoring is received via the Ophthalmology Assessment Form, your next prescription must be written to taper *(insert name)* off of SABRIL, as no additional refills will be provided following completion of the taper.

This letter serves to remind you of the potential issues surrounding the abrupt withdrawal of SABRIL and provides the medication tapering recommendations from the Withdrawal of Sabril Therapy Section of the approved labeling.

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- Days 7-10: 25 mg/kg/day (12.5 mg/kg BID)
- Day 11: Vigabatrin completely discontinued

Read the full Prescribing Information in the approved labeling for additional details.

Please provide SHARE Call Center with your patient's Ophthalmology Assessment Form as soon as possible. The Ophthalmology Assessment form is available through S.H.A.R.E. program at www.lundbeckshare.com or the S.H.A.R.E Central Call Center. Please call the S.H.A.R.E call center at 1-888-45-SHARE with any questions, concerns, or updates regarding this patient.

Other medical inquiries should be directed to the Lundbeck Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Lundbeck Patient Safety Department at 1-800-455-1141.

April 7, 2009

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Sincerely,

Lundbeck Inc.

April 7, 2009

Sabril®
vigabatrin
500 mg tablet
500 mg powder for oral solution

PRESCRIBER ENROLLMENT AND AGREEMENT FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

Attestation of Knowledge of Sabril

By signing below and completing the form below and on page 2, I acknowledge that I have read and understand the information in the Sabril Prescribing Information, and I agree to be registered in the SHARE program.

- Sabril is only approved for pediatric patients with infantile spasms (IS) 1 month to 2 years of age or for adults with refractory complex partial seizures (CPS) who have responded inadequately to several alternative treatments. Sabril is not a first-line treatment for refractory CPS.
- I have experience in treating epilepsy.
- I know the risks of Sabril treatment, specifically vision loss.
- *For physicians who prescribe Sabril for IS:* I have knowledge of the risk of T2 MRI abnormality in infants with IS.
- I understand that the effectiveness of Sabril in treating seizures can be assessed within 2 to 4 weeks of initiating therapy in infants and within 12 weeks of initiating therapy in adults. The possibility that vision loss can worsen despite discontinuation of Sabril has not been excluded. In patients with no meaningful improvement in seizure control, Sabril must be discontinued. For patients with meaningful seizure improvement, clinicians and patients need to have continuing discussions of benefit-risk for the duration of therapy.
- I must order and review visual assessment testing at baseline (within 4 weeks of Sabril initiation), at least every 3 months after initiation while on Sabril, and approximately 3 to 6 months after discontinuation of Sabril.
- I will educate patients/parents/legal guardians considering treatment with Sabril on the benefits and risks of the drug, give them a copy of the *Medication Guide*, instruct them to read it, and encourage them to ask questions.
- After reviewing the *Medication Guide* with the patient/parent/legal guardian and prior to the initial prescription, I may use the *Patient/Parent/Legal Guardian-Physician Agreement Form* to reinforce the education provided.
- I will counsel patients who fail to comply with the SHARE program requirements.
- I will remove patients from Sabril therapy who fail to comply with SHARE program requirements after appropriate counseling.
- I understand that Sabril is not available at retail pharmacies. Sabril is only available through select specialty pharmacies.
- I understand that all initial prescriptions for Sabril must go through the SHARE Call Center (1-888-45-SHARE [1-888-457-4273]) and will then be fulfilled by a specialty pharmacy.
- Prior to dispensing any Sabril prescription, I understand that SHARE will verify that I have a signed copy of this *Prescriber Enrollment and Agreement Form* on file.
- I will report all serious adverse events with Sabril to Lundbeck Inc. at 1-800-455-1141 or to the US Food and Drug Administration at 1-800-FDA-1088.

Prescriber Name _____ _____ _____
Last First MI

Prescriber Degree ☐ **MD** ☐ **DO** **Signature** _____ **Date** _____
month/day/year

Attestation continues on page 2

Sabril®
vigabatrin
500 mg tablet
500 mg powder for oral solution

PRESCRIBER ENROLLMENT AND AGREEMENT FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

Attestation continued from page 1

Attestation of Knowledge of Sabril

For additional information, please visit www.LundbeckSHARE.com or call the SHARE Call Center at 1-888-45-SHARE (1-888-457-4273).

Prescriber Name _____

Institution Name (if applicable) _____

Prescriber Address _____ (Street) _____ (City) _____ (State) _____ (ZIP Code)

Telephone Number _____ (Area Code) (Telephone Number)

Alternative Telephone Number _____ (Area Code) (Telephone Number)

Office Fax _____ (Area Code) (Fax Number)

E-mail _____

Prescriber NPI# _____

Specialty

- ☐ **Epileptology**
- ☐ **Pediatric Neurology**
- ☐ **Other** _____
- ☐ **Neurology**
- ☐ **Internal Medicine**

Office Contact Name _____ (Last) _____ (First)

Second Contact Name _____ (Last) _____ (First)

By completing and submitting this form, you will be registered in the SHARE program and may begin prescribing Sabril.

For additional information, please visit www.LundbeckSHARE.com or call the SHARE Call Center at 1-888-45-SHARE (1-888-457-4273).

Once registered in the SHARE program, you will receive a copy of the *Sabril Starter Kit*, which will contain the complete Prescribing Information, information on the SHARE program, the *Medication Guide*, and the *Patient/Parent/Legal Guardian-Physician Agreement* to be used when initiating Sabril therapy. Additional copies of the *Sabril Starter Kit* can be obtained by contacting your Lundbeck Account Manager or contacting the SHARE Call Center (1-888-45-SHARE).

You only need to register in the SHARE program once, and you are under no obligation to prescribe Sabril.

To complete your registration, fax both pages of your completed *Prescriber Enrollment and Agreement Form* to SHARE at 1-877-742-1002.

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E
Support, Help And Resources for Epilepsy

STEP ONE: Patient Profile

Name (First, Middle, Last): _____ Sex: ❑ Male ❑ Female DOB: _____ month/day/year

Address: _____ City: _____ State: _____ Zip Code: _____

SSN: _____-_____-_____ Phone: _____ Today's Date: _____ month/day/year

Sabril Administration Site: ❑ Home ❑ Hospital ❑ I/DD Facility

I authorize my healthcare providers and health plans to disclose personal and medical information related to my use or potential use of Sabril (vigabatrin) to Lundbeck and its agents and contractors and I authorize Lundbeck to use and disclose this information to: 1) establish my benefit eligibility; 2) communicate with my healthcare providers and health plans about my benefit and coverage status and my medical care; 3) provide support services, including facilitating the provision of Sabril to me; 4) evaluate the effectiveness of Sabril's education programs; and 5) participate in the Sabril Patient Registry. I agree that using the contact information I provide, Lundbeck may get in touch with me for reasons related to the SHARE program and may leave messages for me that disclose that I take Sabril.

I understand that once my health information has been disclosed to Lundbeck, privacy laws may no longer restrict its use or disclosure; however, Lundbeck agrees to protect my information by using and disclosing it only for the purposes described above or as required by law. I may also cancel this authorization in the future by notifying Lundbeck in writing and submitting it by fax to 1-877-742-1002 or by calling 1-888-45-SHARE (1-888-457-4273). If I cancel, Lundbeck will cease using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in the SHARE program. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me. I also certify that the information provided about the insurance status is complete and accurate and will update the SHARE Call Center promptly if such status should change.

Power of Attorney: ❑ Yes ❑ No ❑ N/A Power of Attorney (First, Middle, Last): _____

Patient / Parent / Legal Guardian Signature: _____ Date: _____ month/day/year

STEP TWO: Patient Insurance Profile

Name of Primary Payer: _____ Phone Number: _____

Relationship to Cardholder: ❑ Self ❑ Spouse ❑ Child ❑ Other

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Name of Secondary Payer: _____ Phone Number: _____

Relationship to Cardholder: ❑ Self ❑ Spouse ❑ Child ❑ Other

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Prescription Benefit Manager: _____ Phone Number: _____

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Lundbeck

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

STEP THREE: Prescriber Information

Prescriber's Name (First, Middle Initial, Last): _____ NPI #: _____

Prescriber Address: _____

City: _____ State: _____ Zip: _____

Phone Number: _____ Fax: _____

❑ I have completed the Prescriber Enrollment and Agreement Form required for prescribing Sabril.

I certify that I have reviewed the Medication Guide with the patient/parent/legal guardian, and have counseled him/her on the risks of SABRIL, including vision loss. I commit to ordering and reviewing visual testing at the appropriate intervals in accordance with the SABRIL full prescribing information.

I authorize TheraCom, LLC. in its capacity on behalf of Lundbeck Inc. to be my designated agent and to act as my business associate (as defined in 45 CFR 160.103) to use and disclose any information in this form to the insurer of the above-named patient and to obtain any information about the patient, including any protected health information (as defined in 45 CFR 160.103), from the insurer, including eligibility and other benefit coverage information, for my payment and/or health care operation purposes. As my business associate, TheraCom is required to comply with, and by its signature hereto, agrees that it will comply with, the applicable requirements of 45 CFR 164.504(e) regarding business associates, and that it will safeguard any protected health information that it obtains on my behalf, and will use and disclose this information only for the purposes specified herein or as otherwise required by law.

Prescriber Signature: _____ Date: _____
No Stamped Signature month/day/year

TheraCom Signature: _____ Date: _____
month/day/year

STEP FOUR: Prescription Information

Prescription: Sabril ❑ 500 mg tablets ❑ 500 mg powder for oral solution*† Quantity: _____ (_____) Tablets/Packets
(Digits and written words)

*Child Weight (kg): _____ Date: _____ Refills: _____ (_____)
month/day/year *(Digits and written words)*

SIG: _____

Primary ICD-9 Code: _____ Secondary ICD-9 Code: _____

Instructions: Ship to: ❑ Patient home (address in Step One) ❑ Other (address below) †*Add ancillary supplies as needed*

Patient Name: _____ Address: _____

City: _____ State: _____ Zip: _____ Phone: _____

Consultant ophthalmic professional: _____ Scheduled date of baseline visual assessment _____
month/day/year

Prescriber Signature: _____ Date: _____
month/day/year

Lundbeck

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

STEP FIVE: Patient History

Name (First, Middle, Last):_____ DOB:_____ (month/day/year) Today's Date: _____ (month/day/year)

Race *(Check only one)*: ❑ American Indian or Alaska Native ❑ Asian ❑ Black or African American ❑ Native Hawaiian or Other Pacific Islander ❑ Caucasian ❑ Hispanic ❑ Other

History of Sabril Use:

Is the patient currently taking Sabril? ❑ Yes ❑ No

Has the patient previously taken Sabril? ❑ Yes ❑ No

If the patient has taken or is taking Sabril, how long were they on drug?

_____day(s) (Number) _____week(s) (Number) _____month(s) (Number) _____year(s) (Number)

Reason for Use: ❑ CPS ❑ IS ❑ Other, Specify:_____

If IS, what is the etiology: ❑ Cryptogenic ❑ Symptomatic - TS ❑ Symptomatic, Other

Please check all agents previously or currently utilized by the patient:

Previously Taken	Currently Taking	
❑	❑	Phenytoin
❑	❑	Lamotrigine
❑	❑	Felbamate
❑	❑	Depakote/Valproic acid
❑	❑	Topiramate
❑	❑	Tiagabine
❑	❑	Zonisamide
❑	❑	Levetiracetam
❑	❑	Carbamazepine
❑	❑	Oxcarbazepine
❑	❑	Benzodiazepine(s)
❑	❑	ACTH
❑	❑	Other steroids, specify:_____
❑	❑	OTHER, specify: _____

Please check the # of monotherapy trials by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

Please check the # of trials with 2 agents by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

Please check the # of trials with 3 or more agents by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

www.LundbeckSHARE.com
Fax to 1-877-742-1002

Lundbeck

Sabril®
vigabatrin
500 mg tablet
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S·H·A·R·E®
Support, Help And Resources for Epilepsy

TREATMENT MAINTENANCE FORM

Because the risk of vision loss increases over time with continued use, it is essential to assess a patient's response to Sabril early and determine that the benefit in treating the patient's seizures with Sabril is clinically meaningful and outweighs the risk of continued therapy with it.

You are therefore asked to attest to the following:

- That you have assessed your patient's response to Sabril
- That you have discussed the benefits and risks of continued Sabril therapy with the patient, parent, and/or legal guardian
- That you have determined in your professional judgment that the benefit of controlling seizures exceeds the risk of vision loss
- That continued Sabril therapy is appropriate and warranted

❑ I have evaluated my patient's clinical response to the recent initiation of Sabril treatment and have verified a clinically meaningful improvement in seizure control. I have determined that the benefit of Sabril treatment outweighs the risk of vision loss at this time. I recommend that my patient continue maintenance therapy with Sabril.

Patient name (First, Middle, Last): _____

Patient DOB: _____
month/day/year

Prescriber name: _____ Prescriber NPI #: _____

Signature: _____ Date: _____
month/day/year

www.LundbeckSHARE.com

Lundbeck

Fax to 1-877-742-1002

Lundbeck Inc., Four Parkway North, Deerfield, IL 60015.

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

OPHTHALMOLOGIC ASSESSMENT FORM

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Support, Help And Resources for Epilepsy

To be completed by the prescribing neurologist with each ophthalmologic assessment.

STEP ONE: Patient Profile

Name (First, Middle, Last) _____ Sex: ❒ Male ❒ Female DOB _____
month/day/year

Address _____ City _____ State _____ ZIP _____

Patient currently on Sabril: ❒ Yes ❒ No

STEP TWO: Consultant Ophthalmic Professional

Ophthalmic Professional Name (First, Middle Initial, Last) _____ NPI #_____

Ophthalmic Professional Address _____

City _____ State_____ ZIP_____

Phone _____

STEP THREE: Ophthalmologic Assessment

Taking into account benefit-risk considerations, the performance of ophthalmologic assessment will be enforced for all patients, and the drug will not continue to be dispensed unless this required documentation is completed and faxed to the SHARE Call Center at 1-877-742-1002.

Section 1

1. Was an ophthalmologic assessment conducted? ❒ Yes _____ ❒ No *(If no, go to Section 2 on next page)*
month/day/year

2. If yes, was a visual acuity evaluation conducted? ❒ Yes ❒ No

What were the results? Left eye _____/_____ Right eye _____/_____

3. Was kinetic perimetry conducted? ❒ Yes ❒ No

What were the results? Degree of retained visual field to V4e target (each eye):

- ❒ >160° retained
- ❒ 120° to 160° retained
- ❒ 60° to <120° retained
- ❒ 40° to <60° retained
- ❒ 20° to <40° retained
- ❒ 10° to <20° retained
- ❒ <10° retained

4. Was static perimetry conducted? ❒ Yes ❒ No

Specify test program used:_____

What were the results? Concentric/partly concentric pattern of decreased sensitivity occurring within:

- ❒ 60°
- ❒ 40°
- ❒ 20°
- ❒ 10°

Assessment form continues on page 2

Assessment form continued from page 1

5. Was OCT conducted? ❒ Yes ❒ No

What were the results? ❒ Normal
❒ Abnormal

6. Was ERG conducted? ❒ Yes ❒ No

What were the results? ❒ Normal
❒ Abnormal

7. Other testing

Specify test:_____

What were the results? ❒ Normal
❒ Abnormal

Section 2

❒ **An ophthalmologic assessment was not conducted on the patient for the following reason(s):**

❒ Patient is blind

❒ Patient's general neurological condition precludes the need for visual assessment

❒ Patient's medical condition prevents visual assessment being performed safely *(please explain)*_____

_____

❒ Other *(please explain)* _____

Section 3

If the assessment occurred more than 1 month after the due date, please indicate the reason:

❒ Patient's financial/reimbursement situation

❒ Transportation issues

❒ Scheduling conflicts

❒ Other *(please explain)* _____

Prescriber's Name _____ *Prescriber's NPI #* _____

Signature _____ *Date* _____
month/day/year

If formal perimetry was conducted, please attach a copy of the visual field recordings.

www.LundbeckSHARE.com Lundbeck ***Fax to 1-877-742-1002***

Lundbeck Inc., Four Parkway North, Deerfield, IL 60015.

COMPLEX PARTIAL SEIZURES (CPS)

Patient/Parent/Legal Guardian–Physician Agreement for Sabril® (vigabatrin) Use

Completed forms must be faxed to the SHARE Call Center (1-877-742-1002) at treatment initiation. Place the original signed document in the patient's medical record and provide a copy to the patient, parent, or legal guardian.

Identification of Signer:

Patient—I, _____, am the patient. I am able to read and understand this document and will sign for myself.

Parent/Legal Guardian—I am not the patient. I am the parent/legal guardian of _____, who is the patient. I am able to read and understand this document and will sign on behalf of the patient.

To use Sabril appropriately, the patient/parent/legal guardian should:

- **Be aware that Sabril causes a serious vision problem in some people.**
- **Read the *Medication Guide* to understand the risks of Sabril therapy.**
- **Talk with your doctor about the information you receive before signing the *Patient/Parent/Legal Guardian-Physician Agreement*.**
- **Report any problems you might experience when using Sabril to your doctor as soon as they happen.**
- **Visit the doctor regularly to make sure that Sabril continues to be right for you to take.**

This agreement is to be completed and signed by the patient/parent/legal guardian and the doctor. The person who signs is to read each item below and initial in the space provided if the item is understood. After initialing each item, the signature goes at the end of this agreement. The signer is not to sign this agreement or take Sabril if there are any unanswered questions.

1. I, _____, have read the *Sabril Medication Guide*. My doctor has explained the risks.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

2. I understand that Sabril is a medicine used to treat complex partial seizures that have not responded to several other treatments. The doctor and I have talked about my treatment choices and have decided that treatment with Sabril is right for me.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

3. I understand that about 1 in 3 adult patients taking Sabril have damage to their vision. I understand that if any vision loss occurs, it will not improve even if Sabril is stopped.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

4. I understand that there is no way to tell if I will develop vision loss.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

5. I understand that vision tests required by the doctor when starting Sabril treatment must be obtained. This testing will continue as long as Sabril is taken and after stopping therapy. I understand that these tests will not prevent vision loss. However, by stopping the treatment as a result of these tests, the amount of vision loss may be limited. I understand that it is important to see the doctor on a regular basis to make sure that Sabril continues to be right for me to take.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

6. The doctor and I have talked about my epilepsy. We have also talked about the potential benefits and risks of taking Sabril. We have agreed that Sabril therapy will be started, and that the initial treatment with Sabril will consist of an Evaluation Phase of about 3 months.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

7. If the seizures are not better during the Evaluation Phase, Sabril® (vigabatrin) therapy must be stopped. If seizure control has improved, I will discuss with the doctor the potential benefits and risks of continuing Sabril therapy (the Maintenance Phase). I understand that the risk of vision loss will continue as long as I continue to take Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

8. I understand that Sabril will be prescribed for myself, my son or daughter, or my legal ward only. I will not share Sabril with other people.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

9. The doctor has discussed with me other treatments for my epilepsy. We have decided that Sabril is the right treatment for me. I understand that Sabril can be discontinued at any time. I also know that I cannot stop taking Sabril without my doctor telling me to do so. I agree to tell the doctor if I decide to stop taking Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

10. All my questions were answered to my satisfaction. I now authorize the doctor, _____, to begin treatment with Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

I have read and understood all of the information presented above and agree to use Sabril therapy.

Patient/Parent/Legal Guardian Agreement

Evaluation Phase

To be signed by patient/parent/legal guardian upon initiation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Maintenance Phase

To be signed by patient/parent/legal guardian upon continuation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Physician Agreement

I, _____, have fully explained to the patient/parent/legal guardian the potential benefits and risks of Sabril treatment. I have provided the patient/parent/legal guardian with the brochure entitled *Sabril Medication Guide*, and have answered all questions regarding therapy with Sabril.

Evaluation Phase

To be signed by physician upon initiation of Sabril therapy.

Signature:_____ Date_____ (month/day/year)

Maintenance Phase

To be signed by physician upon continuation of Sabril maintenance therapy.

Signature:_____ Date_____ (month/day/year)

Fax to the SHARE Call Center (1-877-742-1002)

INFANTILE SPASMS (IS)

Parent/Legal Guardian–Physician Agreement for Sabril® (vigabatrin) Use

Completed forms must be faxed to the SHARE Call Center (1-877-742-1002) at treatment initiation. Place the original signed document in the patient's medical record and provide a copy to the patient, parent, or legal guardian.

To use Sabril appropriately, you should:

- **Be aware that Sabril causes a serious vision problem in some people.**
- **Be aware that there have been reports of changes in the brain images of some patients with infantile spasms on Sabril. The importance of these changes is not known.**
- **Read the *Medication Guide* to understand the risks of Sabril therapy.**
- **Talk with your doctor about the information you receive before signing the *Parent/Legal Guardian-Physician Agreement.***
- **Report any problems your infant might experience when using Sabril to your infant's doctor as soon as they happen.**
- **Visit your infant's doctor regularly to make sure that Sabril continues to be right for your infant to take.**

This agreement is to be completed and signed by the parent/legal guardian and the doctor. Read each item below and initial in the space provided if you understand the item. After you have initialed each item, sign your name at the end of this agreement. Do not sign this agreement or have your infant take Sabril if you have any unanswered questions.

1. I, _____, have read the *Sabril Medication Guide*. My infant's doctor has explained the risks.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

2. I understand that Sabril is a medicine used to treat infantile spasms. My infant's doctor and I have talked about my infant's treatment. We both think that Sabril should be used to treat my infant.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

3. I understand that about 1 in 3 infants taking Sabril will have damage to their vision. I understand that if any vision loss occurs, it will not improve even if my infant stops taking Sabril.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

4. I understand that there is no way to tell if my infant will develop vision loss.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

5. I understand that vision tests required by my infant's doctor when starting Sabril treatment must be obtained for my infant. This testing will continue as long as Sabril is taken and after stopping therapy. I understand that these tests will not prevent vision loss. However, by stopping the treatment as a result of these tests, the amount of vision loss may be limited. I understand that it is important to take my infant to see his or her doctor on a regular basis to make sure that Sabril continues to be right for them to take.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

6. I understand that there have been reports of a change in the brain pictures of infants taking Sabril. The change may reverse by itself or when the Sabril dose is lowered or is stopped. It is not known if this change has any effect on the infant.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

7. I understand that my infant's doctor may want to take an MRI or picture of my infant's brain before starting or during Sabril treatment.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

8. My infant's doctor and I have talked about my infant's epilepsy. We have talked about Sabril® (vigabatrin) as a treatment option for my infant. We have agreed that Sabril therapy will be started, and that the initial treatment with Sabril will consist of an Evaluation Phase of about 1 month.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

9. If my infant's seizures are not better during the Evaluation Phase, Sabril therapy must be stopped. If my infant's seizure control has improved, I will discuss with his or her doctor the potential benefits and risks of continuing Sabril therapy (the Maintenance Phase). I understand that the risk of developing vision loss will continue as long as my infant takes Sabril. I also understand that there may be some chance of an MRI change seen in the brain; however, we do not know if this change has any medical significance.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

10. Sabril will be prescribed only for my infant. I will not share his or her Sabril with other people.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

11. We have decided that Sabril is the most appropriate treatment for my infant. I understand that my infant can stop taking Sabril at any time. However, I will not have my infant abruptly stop using Sabril unless instructed to do so by his or her doctor. If treatment is abruptly stopped, my infant's seizures might increase or return. I agree to tell my doctor if I decide to stop giving Sabril to my infant.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

12. All my questions were answered to my satisfaction. I now authorize my doctor, _____, to begin my infant's treatment with Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

I have read and understood all of the information presented above and agree to use Sabril therapy.

Parent/Legal Guardian Agreement

Evaluation Phase

To be signed by parent/legal guardian upon initiation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Maintenance Phase

To be signed by parent/legal guardian upon continuation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Physician Agreement

I, _____, have fully explained to the parent/legal guardian the potential benefits and risks of Sabril treatment. I have provided the parent/legal guardian with the brochure entitled *Sabril Medication Guide*, and have answered all questions regarding therapy with Sabril.

Evaluation Phase

To be signed by physician upon initiation of Sabril therapy.

Signature:_____ Date_____ (month/day/year)

Maintenance Phase

To be signed by physician upon continuation of Sabril maintenance therapy.

Signature:_____ Date_____ (month/day/year)

Fax to the SHARE Call Center (1-877-742-1002)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
08/21/2009

Attachment C

[Package Inserts]

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SABRIL safely and effectively. See full prescribing information for SABRIL.

Sabril® (vigabatrin) Tablets ℞ **Only**
For Oral Administration Only
Initial U.S. Approval: 2009

WARNING: VISION LOSS
See full prescribing information for complete boxed warning

- SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity.
- Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss
- Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL
- Periodic vision testing is required for patients on SABRIL, but cannot reliably prevent vision damage
- Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program

----------INDICATIONS AND USAGE----------

SABRIL is an antiepileptic drug (AED) indicated for:

- **Refractory Complex Partial Seizures in Adults** (1.1). It should be used as adjunctive therapy in patients who have responded inadequately to several alternative treatments.

----------DOSAGE AND ADMINISTRATION----------

- Refractory Complex Partial Seizures in Adults: Initiate therapy at 500 mg twice daily, increasing total daily dose per instructions. The recommended dose is 1.5 grams twice daily (2.1).
- Dose adjustment recommended in renally impaired patients (2.2)
- Reduce dose gradually upon discontinuation (2.3)

----------DOSAGE FORM AND STRENGTHS----------

Tablet: 500 mg (3.1)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- SABRIL causes permanent vision loss (5.1)
- Abnormal MRI signal changes have been reported in some infants with IS receiving SABRIL (5.3)
- Antiepileptic drugs, including SABRIL, increase the risk of suicidal thoughts and behavior (5.5)
- Dose should be tapered gradually to avoid withdrawal seizures (5.6)
- SABRIL causes anemia (5.7)
- SABRIL causes somnolence and fatigue (5.8)
- SABRIL causes peripheral neuropathy (5.9)
- SABRIL causes weight gain (5.10)
- SABRIL causes edema (5.11)

----------ADVERSE REACTIONS----------

Most common adverse reactions (change of ≥ 5% over placebo) in addition to permanent vision loss in adult controlled trials with vigabatrin were fatigue, somnolence, nystagmus, tremor, vision blurred, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck Inc. at 1-800-455-1141 or www.lundbeckinc.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Decreased phenytoin plasma levels have been reported (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available (8.1)
- Nursing Mothers: SABRIL is excreted in human milk (8.2)
- Renal Impairment: Dose adjustment recommended (2.2, 8.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

Issued: 08/2009

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: VISION LOSS

- SABRIL causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss
- Vision testing at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy is required for adults on SABRIL. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. Once detected, vision loss due to SABRIL is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.
- It is possible that vision loss can worsen despite discontinuation of SABRIL
- Because of the risk of vision loss, SABRIL should be withdrawn from patients who fail to show substantial clinical benefit within 3 months of initiation, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.
- Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient, can still adversely affect function.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks
- The lowest dose and shortest exposure to SABRIL should be used that is consistent with clinical objectives

Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program called SHARE, by calling 1-888-45-SHARE. Only prescribers and pharmacies registered with SHARE may prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE [see WARNINGS AND PRECAUTIONS, Distribution Program for SABRIL (5.2)].

1 INDICATIONS AND USAGE

1.1 Refractory Complex Partial Seizures in Adults

SABRIL® is indicated as adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative

treatments and for whom the potential benefits outweigh the risk of vision loss [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)]. SABRIL is not indicated as a first line agent for complex partial seizures.

2 DOSAGE AND ADMINISTRATION

2.1 Refractory Complex Partial Seizures in Adults

SABRIL 500 mg tablets should be given as twice daily oral administration with or without food. Therapy should be initiated at 1 g/day (500 mg twice daily). Total daily dose may be increased in 500 mg increments at weekly intervals depending on response. The recommended dose of SABRIL in adults is 3 g/day (1.5 g twice daily). A 6 g/day dose has not been shown to confer additional benefit compared to the 3 g/day dose and is associated with an increased incidence of adverse events.

2.2 Patients with Renal Impairment

SABRIL is primarily eliminated through the kidney. In patients with renal impairment, dose adjustments should be made as follows:

In patients with mild renal impairment (CLcr >50 to 80 mL/min), the dose should be decreased by 25%; in patients with moderate renal impairment (CLcr >30 to 50 mL/min), the dose should be decreased by 50%; and in patients with severe renal impairment (CLcr >10 to <30 mL/min), the dose should be decreased by 75%.

CLcr in mL/min may be estimated from a serum creatinine (mg/dL) determination using the following formula:

CLcr *= [140-*age* (*years*)] *weight* (*kg*)/72 *serum creatinine* (*mg/dL*)]
*[0.85 *for female patients*]

The effect of dialysis on SABRIL clearance has not been adequately studied.

[see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5)].

2.3 General Dosing Considerations

SABRIL should be withdrawn gradually. In controlled clinical studies in adults with CPS, vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6)].

3 DOSAGE FORMS AND STRENGTHS

3.1 Tablet

500 mg Tablet.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Vision Loss (see BOXED WARNING)

Because of the risk of vision loss and because SABRIL, when it is effective, provides an observable symptomatic benefit, a patient who fails to show substantial clinical benefit within 3 months of initiation of treatment, should be withdrawn from SABRIL. If in the clinical judgment of the prescriber evidence of treatment failure becomes obvious earlier than 3 months, treatment with SABRIL should be discontinued at that time. Patient response to and continued need for treatment should be periodically assessed.

Monitoring of Vision
Monitoring of vision by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina is required. Vision testing at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months is required for adults on SABRIL. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.

The diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor vision periodically must be documented under the SHARE program. Perimetry is recommended, preferably by automated threshold visual field testing. Additional testing may also include electrophysiology (e.g., electroretinography [ERG]), retinal imaging (e.g., optical coherence tomography [OCT]), and/or other methods appropriate for the patient. In patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate patient counseling and with documentation in the SHARE program of the inability to test vision. Because of variability, results from ophthalmic monitoring must be interpreted with caution, and repeat testing is recommended if results are abnormal or uninterpretable. Repeat testing in the first few weeks of treatment is recommended to establish if, and to what degree, reproducible results can be obtained, and to guide selection of appropriate ongoing monitoring for the patient.

The onset and progression of vision loss from SABRIL is unpredictable, and it may occur or worsen precipitously between tests. Once detected, vision loss due to SABRIL is not reversible. It is expected that even with frequent monitoring, some SABRIL patients will develop severe vision loss.

5.2 Distribution Program for SABRIL
SABRIL is available only under a special restricted distribution program called the SHARE program. Under the SHARE program, only prescribers and pharmacies

registered with the program are able to prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE. Contact the SHARE program at 1-888-45-SHARE.

To enroll in SHARE, prescribers must understand the risks of SABRIL and complete the SHARE Prescriber Enrollment and Agreement Form indicating agreement to:

- Enroll all patients in SHARE
- Review the SABRIL Medication Guide with every patient
- Educate patients on the risks of SABRIL, including the risk of vision loss [see BOXED WARNING: VISION LOSS]
- Order and review vision assessments at initiation of SABRIL treatment and every 3 months during therapy
- Remove patients from SABRIL therapy if the patients do not experience meaningful reduction in seizures
- Counsel patients who fail to comply with the program requirements
- Remove patients from SABRIL therapy who fail to comply with the program requirements after appropriate counseling

5.3 Magnetic Resonance Imaging (MRI) Abnormalities

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for Infantile Spasms (IS) with vigabatrin. In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 21.5% in vigabatrin-treated patients versus 4.1% in patients treated with other therapies.

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment. In a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied.

Neurotoxicity (including convulsions and hypomyelination) was observed in rats exposed to vigabatrin during late gestation and the neonatal and juvenile periods of development. The relationship between these findings and the abnormal MRI findings in infants treated for IS with vigabatrin is unknown [see WARNINGS AND PRECAUTIONS, Neurotoxicity (5.4) and USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)].

The specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with vigabatrin for CPS. In a blinded review of MRI images obtained in prospective clinical trials in patients with CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo patients.

For adults treated with SABRIL, routine MRI surveillance is unnecessary as there is no evidence that vigabatrin causes MRI changes in this population.

5.4 Neurotoxicity

Vacuolization, characterized by fluid accumulation and separation of the outer layers of myelin, has been observed in brain white matter tracts in adult and juvenile rats and adult mice, dogs, and possibly monkeys following administration of vigabatrin. This lesion, referred to as intramyelinic edema (IME), was seen in animals at doses within the human therapeutic range. A no-effect dose was not established in rodents or dogs. In the rat and dog, vacuolization was reversible following discontinuation of vigabatrin treatment, but, in the rat, pathologic changes consisting of swollen or degenerating axons, mineralization, and gliosis were seen in brain areas in which vacuolation had been previously observed. Vacuolization in adult animals was correlated with alterations in MRI and changes in visual and somatosensory evoked potentials (EP).

Administration of vigabatrin to rats during the neonatal and juvenile periods of development produced vacuolar changes in the gray matter (areas including the thalamus, midbrain, deep cerebellar nuclei, substantia nigra, hippocampus, and forebrain) which are considered distinct from the IME observed in vigabatrin treated adult animals. Decreased myelination, retinal dysplasia, and neurobehavioral abnormalities (convulsions, neuromotor impairment, learning deficits) were also observed following vigabatrin treatment of young rats. These effects occurred at doses associated with plasma vigabatrin levels substantially lower than those achieved clinically in infants and children.

In a published study, vigabatrin (200, 400 mg/kg/day) induced apoptotic neurodegeneration in the brain of young rats when administered by intraperitoneal injection on postnatal days 5-7.

Administration of vigabatrin to female rats during pregnancy and lactation at doses below those used clinically resulted in hippocampal vacuolation and convulsions in the mature offspring.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3)].

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including SABRIL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing SABRIL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert

for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, SABRIL should be withdrawn gradually. In controlled clinical studies in adults with CPS, SABRIL was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued [see DOSAGE AND ADMINISTRATION, General Dosing Considerations (2.3), PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.4)].

5.7 Anemia

In North American controlled trials, 5.7% of patients (16/280) receiving SABRIL and 1.6% of patients (3/188) receiving placebo had adverse events of anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled trials, there were mean decreases in hemoglobin of about 3% and 0% in SABRIL and placebo-treated patients, respectively, and in hematocrit of about 1% in Sabril treated patients compared to a gain of about 1% in patients treated with placebo.

In controlled and open label epilepsy trials, 3 SABRIL patients (0.06%, 3/4855) discontinued for anemia and 2 SABRIL patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or hematocrit below 24%.

5.8 Somnolence and Fatigue

SABRIL causes somnolence and fatigue. Patients should be advised not to drive a car or operate other complex machinery until they are familiar with the effects of SABRIL on their ability to perform such activities.

Pooled data from two SABRIL controlled trials demonstrated that 24% (54/222) of SABRIL patients experienced somnolence compared to 10% (14/135) of placebo patients. In those same studies, 28% of SABRIL patients experienced fatigue compared to 15% (20/135) of placebo patients. Almost 1% of SABRIL patients discontinued from clinical trials for somnolence and almost 1% discontinued for fatigue.

5.9 Peripheral Neuropathy

SABRIL causes symptoms of peripheral neuropathy. In a pool of North American controlled and uncontrolled epilepsy studies, 4.2% (19/457) of SABRIL patients developed signs and/or symptoms of peripheral neuropathy. In the subset of North American placebo-controlled epilepsy trials, 1.4% (4/280) of SABRIL treated patients and no (0/188) placebo patients developed signs and/or symptoms of peripheral neuropathy. Initial manifestations of peripheral neuropathy in these trials included, in some combination, symptoms of numbness or tingling in the toes or feet, signs of reduced distal lower limb vibration or position sensation, or progressive loss of

reflexes, starting at the ankles. Clinical studies in the development program were not designed to investigate peripheral neuropathy systematically and did not include nerve conduction studies, quantitative sensory testing, or skin or nerve biopsy. There is insufficient evidence to determine if development of these signs and symptoms were related to duration of SABRIL treatment, cumulative dose, or if the findings of peripheral neuropathy were completely reversible upon discontinuation of SABRIL.

5.10 Weight Gain

SABRIL causes weight gain. Data pooled from randomized controlled trials found that 17% (77/443) of SABRIL patients versus 8% (22/275) of placebo patients gained ≥ 7% of baseline body weight. In these same trials, the mean weight change among SABRIL patients was 3.5 kg compared to 1.6 kg for placebo patients. In all epilepsy trials, 0.6% (31/4855) of SABRIL patients discontinued for weight gain. The long term effects of SABRIL related weight gain are not known. Weight gain was not related to the occurrence of edema.

5.11 Edema

SABRIL causes edema. Pooled data from controlled trials demonstrated increased risk among SABRIL patients compared to placebo patients for peripheral edema (SABRIL 2%, placebo 1%), and edema (SABRIL 1%, placebo 0%). In these studies, one SABRIL and no placebo patients discontinued for an edema related AE. There was no apparent association between edema and cardiovascular adverse events such as hypertension or congestive heart failure. Edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

6 ADVERSE REACTIONS

SABRIL causes permanent damage to vision in a high percentage of patients [see BOXED WARNING: VISION LOSS and WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in U.S. and Primary Non-U.S. Clinical Studies

In U.S. and primary non-U.S. clinical studies of 4,079 SABRIL treated patients, the most commonly observed (≥ 5%) adverse reactions associated with the use of SABRIL in combination with other AEDs were headache (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsion (11%), nasopharyngitis (10%), weight increased (10%), upper respiratory tract infection (10%), visual field defect (9%), depression (8%), tremor (7%), nystagmus (7%), nausea (7%), diarrhea (7%),

memory impairment (7%), insomnia (7%), irritability (7%), coordination abnormal (7%), vision blurred (6%), diplopia (6%), vomiting (6%), influenza (6%), pyrexia (6%), and rash (6%).

The adverse reactions most commonly associated with SABRIL treatment discontinuation in ≥ 1% of patients were convulsion (1.4%) and depression (1.5%).

Most Common Adverse Reactions in Controlled Clinical Trials

Refractory Complex Partial Seizures in Adults
Table 2 lists the treatment emergent adverse reactions that occurred in ≥ 2% and more than one patient per SABRIL-treated group and that occurred more frequently than in placebo patients from 2 U.S. add-on clinical studies of refractory CPS in adults.

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥ 2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Ear Disorders			
Tinnitus	3 (2)	0 (0)	2 (1)
Vertigo	3 (2)	2 (5)	2 (1)
Eye Disorders			
Vision blurred	18 (13)	7 (16)	7 (5)
Diplopia	9 (7)	7 (16)	4 (3)
Asthenopia	3 (2)	1 (2)	0 (0)
Eye pain	0 (0)	2 (5)	0 (0)
Gastrointestinal Disorders			
Diarrhoea	14 (10)	7 (16)	10 (7)
Nausea	13 (10)	1 (2)	11 (8)
Vomiting	9 (7)	4 (9)	8 (6)
Constipation	11 (8)	2 (5)	4 (3)
Abdominal pain upper	7 (5)	2 (5)	2 (1)
Dyspepsia	6 (4)	2 (5)	4 (3)
Stomach discomfort	5 (4)	1 (2)	1 (1)
Abdominal pain	4 (3)	1 (2)	2 (1)
Toothache	3 (2)	2 (5)	3 (2)
Abdominal distension	3 (2)	0 (0)	1 (1)
General Disorders			
Fatigue	31 (23)	17 (40)	21 (16)
Gait disturbance	8 (6)	5 (12)	9 (7)
Asthenia	7 (5)	3 (7)	2 (1)
Oedema peripheral	7 (5)	3 (7)	1 (1)
Fever	6 (4)	3 (7)	4 (3)
Chest pain	2 (1)	2 (5)	2 (1)
Thirst	3 (2)	0 (0)	0 (0)
Malaise	0 (0)	2 (5)	0 (0)
Infections			

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥ 2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Nasopharyngitis	19 (14)	4 (9)	14 (10)
Upper respiratory tract infection	10 (7)	4 (9)	8 (6)
Influenza	7 (5)	3 (7)	5 (4)
Urinary tract infection	5 (4)	2 (5)	0 (0)
Bronchitis	0 (0)	2 (5)	2 (1)
Injury			
Contusion	4 (3)	2 (5)	3 (2)
Joint sprain	2 (1)	1 (2)	1 (1)
Muscle strain	1 (1)	1 (2)	2 (1)
Wound secretion	0 (0)	1 (2)	0 (0)
Metabolism and Nutrition Disorders			
Increased appetite	2 (1)	2 (5)	1 (1)
Weight increased	8 (6)	6 (14)	4 (3)
Musculoskeletal Disorders			
Arthralgia	14 (10)	2 (5)	4 (3)
Back pain	6 (4)	3 (7)	3 (2)
Pain in extremity	8 (6)	1 (2)	5 (4)
Myalgia	4 (3)	2 (5)	2 (1)
Muscle twitching	1 (1)	4 (9)	2 (1)
Muscle spasms	4 (3)	0 (0)	1 (1)
Nervous System Disorders			
Headache	44 (33)	11 (26)	42 (31)
Somnolence	29 (22)	11 (26)	18 (13)
Dizziness	32 (24)	11 (26)	23 (17)
Nystagmus	17 (13)	8 (19)	12 (9)
Tremor	20 (15)	7 (16)	11 (8)
Memory impairment	9 (7)	7 (16)	4 (3)
Coordination abnormal	10 (7)	7 (16)	3 (2)
Disturbance in attention	12 (9)	0 (0)	1 (1)
Sensory disturbance	6 (4)	3 (7)	3 (2)
Hyporeflexia	6 (4)	2 (5)	1 (1)
Paraesthesia	9 (7)	1 (2)	1 (1)
Lethargy	6 (4)	3 (7)	3 (2)
Hyperreflexia	5 (4)	1 (2)	4 (3)
Hypoaesthesia	5 (4)	2 (5)	2 (1)
Sedation	5 (4)	0 (0)	0 (0)
Status epilepticus	3 (2)	2 (5)	0 (0)
Dysarthria	3 (2)	1 (2)	1 (1)
Postictal state	3 (2)	0 (0)	1 (1)
Sensory loss	0 (0)	2 (5)	0 (0)
Psychiatric Disorders			
Irritability	10 (7)	10 (23)	10 (7)
Depression	8 (6)	6 (14)	4 (3)
Confusional state	5 (4)	6 (14)	1 (1)

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥ 2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Anxiety	6 (4)	0 (0)	4 (3)
Depressed mood	7 (5)	0 (0)	1 (1)
Thinking abnormal	4 (3)	3 (7)	0 (0)
Abnormal behaviour	4 (3)	2 (5)	1 (1)
Expressive language disorder	2 (1)	3 (7)	1 (1)
Nervousness	3 (2)	2 (5)	3 (2)
Abnormal dreams	2 (1)	2 (5)	1 (1)
Reproductive System			
Dysmenorrhoea	12 (9)	2 (5)	4 (3)
Erectile dysfunction	0 (0)	2 (5)	0 (0)
Respiratory and Thoracic Disorders			
Pharyngolaryngeal pain	10 (7)	6 (14)	7 (5)
Cough	3 (2)	6 (14)	9 (7)
Pulmonary congestion	0 (0)	2 (5)	1 (1)
Sinus headache	8 (6)	1 (2)	1 (1)
Skin and Subcutaneous Tissue Disorders			
Rash	6 (4)	2 (5)	6 (4)

6.2 Post Marketing Experience

The following serious adverse events have been reported since approval and use of SABRIL worldwide. All serious adverse events that are not listed above as adverse events reported in clinical trials, that are not relatively common in the population and are not too vague to be useful are listed in this section. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Events are categorized by system organ class.

Birth Defects: Congenital cardiac defects, congenital external ear anomaly, congenital hemangioma, congenital hydronephrosis, congenital male genital malformation, congenital oral malformation, congenital vesicoureteric reflux, dentofacial anomaly, dysmorphism, fetal anticonvulsant syndrome, hamartomas, hip dysplasia, limb malformation, limb reduction defect, low set ears, renal aplasia, retinitis pigmentosa, supernumerary nipple, talipes

Ear: Deafness

Endocrine: Delayed puberty

Gastrointestinal: Gastrointestinal hemorrhage, esophagitis

General: Developmental delay, facial edema, malignant hyperthermia, multi-organ failure

Hepatobiliary: Cholestasis

Nervous System: Dystonia, encephalopathy, hypertonia, hypotonia, muscle spasticity, myoclonus, optic neuritis

Psychiatric: Acute psychosis, apathy, delirium, hypomania, neonatal agitation, psychotic disorder

Respiratory: Laryngeal edema, pulmonary embolism, respiratory failure, stridor

Skin and Subcutaneous Tissue: Angioedema, maculo-papular rash, pruritus

7 DRUG INTERACTIONS

For detailed information about Drug Interactions see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions (12.3).

7.1 Phenytoin

A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies.

7.2 Other AEDs

There are no clinically significant pharmacokinetic interactions between SABRIL and either phenobarbital or sodium valproate. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

7.3 Clonazepam

In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

7.4 Oral Contraceptives

SABRIL is unlikely to affect the efficacy of steroid oral contraceptives.

7.5 Drug-Laboratory Test Interactions

SABRIL decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. In some patients, these enzymes become undetectable. The suppression of ALT and AST activity by SABRIL may preclude the use of these markers, especially ALT, to detect early hepatic injury.

SABRIL may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Vigabatrin produced developmental toxicity, including teratogenic and neurohistopathological effects, when administered to pregnant animals at clinically relevant doses. In addition, developmental neurotoxicity was observed in rats treated with vigabatrin during a period of postnatal development corresponding to the third trimester of human pregnancy. There are no adequate and well-controlled studies in pregnant women. SABRIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of vigabatrin (oral doses of 50 to 200 mg/kg) to pregnant rabbits throughout the period of organogenesis was associated with an increased incidence of malformations (cleft palate) and embryo-fetal death; these findings were observed in two separate studies. The no-effect dose for teratogenicity and embryolethality in rabbits (100 mg/kg) is approximately 1/2 the maximum recommended human dose (MRHD) of 3 g/day on a body surface area (mg/m^2) basis. In rats, oral administration of vigabatrin (50, 100, or 150 mg/kg) throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal anatomic variations. The no-effect dose for embryo-fetal toxicity in rats (50 mg/kg) is approximately 1/5 the MRHD on a mg/m^2 basis. Oral administration of vigabatrin (50, 100, 150 mg/kg) to rats from the latter part of pregnancy through weaning produced long-term neurohistopathological (hippocampal vacuolation) and neurobehavioral (convulsions) abnormalities in the offspring. A no-effect dose for developmental neurotoxicity in rats was not established; the low-effect dose (50 mg/kg) is approximately 1/5 the MRHD on a mg/m^2 basis.

In a published study, vigabatrin (300 or 450 mg/kg) was administered by intraperitoneal injection to a mutant mouse strain on a single day during organogenesis (day 7, 8, 9, 10, 11, or 12). An increase in malformations (including cleft palate) was observed at both doses.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to SABRIL, physicians are advised to recommend that pregnant patients taking SABRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.2 Nursing Mothers

Vigabatrin is excreted in human milk. Because of the potential for serious adverse reactions from vigabatrin in nursing infants [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

The safety and efficacy of SABRIL in pediatric patients (<16 years of age) with CPS has not been established.

Abnormal MRI signal changes were observed in infants [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)].

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

8.4 Geriatric Use

Clinical studies of vigabatrin did not include sufficient numbers of patients aged 65 and over to determine whether they responded differently from younger patients.

Vigabatrin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Oral administration of a single dose of 1.5 g of vigabatrin to elderly (>65 years) patients with reduced creatinine clearance (<50 mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days. The renal clearance of vigabatrin was 36% lower in healthy elderly subjects (>65 years) than in young healthy males. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal

Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.5 Renal Impairment

Dose adjustment, including initiating treatment with a lower dose, is necessary in patients with mild (creatinine clearance >50-80 mL/min), moderate (creatinine clearance >30-50 mL/min) and severe (creatinine clearance >10-30 mL/min) renal impairment [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Class

Vigabatrin is not a controlled substance.

9.2 Abuse

Vigabatrin did not produce adverse events or overt behaviors associated with abuse when administered to humans or animals. It is not possible to predict the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking behavior).

9.3 Dependence

Following chronic administration of vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, vigabatrin should be withdrawn gradually to minimize increased seizure frequency [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6) and PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.4)].

10 OVERDOSAGE

10.1 Signs, Symptoms, and Laboratory Findings of Overdosage

Confirmed and/or suspected vigabatrin overdoses have been reported during clinical trials and in post marketing surveillance. No vigabatrin overdoses resulted in death. When reported, the vigabatrin dose ingested ranged from 3 g to 90 g, but most were between 7.5 g and 30 g. Nearly half the cases involved multiple drug ingestions including carbamazepine, barbiturates, benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine.

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of vigabatrin overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, headache, hypotension, abnormal behavior, increased seizure activity, status epilepticus, and speech disorder. These symptoms resolved with supportive care.

10.2 Treatment or Management for Overdosage

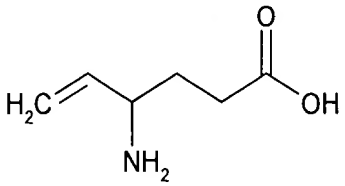
There is no specific antidote for SABRIL overdose. Standard measures to remove unabsorbed drug should be used, including elimination by emesis or gastric lavage. Supportive measures should be employed, including monitoring of vital signs and observation of the clinical status of the patients.

In an *in vitro* study, activated charcoal did not significantly adsorb vigabatrin.

The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

11 DESCRIPTION

Table 3. Description

Proprietary Name:	SABRIL®
Established Name:	Vigabatrin Tablet
Dosage Form:	White, film-coated tablet
Route of Administration:	Oral
Pharmacologic Class of Drug:	Antiepileptic
Chemical Name:	(±) 4-amino-5-hexenoic acid
Structural Formula:	

SABRIL (vigabatrin) is available as a white, film-coated tablet for oral administration. Each tablet contains 500 mg vigabatrin. Tablets also contain as inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide.

Vigabatrin is an oral antiepileptic drug with the chemical name (±) 4-amino-5-hexenoic acid. It is a racemate consisting of two enantiomers. The molecular formula is $C_6H_{11}NO_2$ and the molecular weight is 129.16.

Vigabatrin is a white to off-white powder which is freely soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n-octanol/water partition coefficient of vigabatrin is about 0.011 (log *P*=-1.96) at physiologic pH. Vigabatrin melts with decomposition in a 3-degree range within the temperature interval of 171°C to 176°C. The dissociation constants (pK_a) of vigabatrin are 4 and 9.7 at room temperature (25°C).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the central nervous system.

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

12.2 Pharmacodynamics

Effects on Electrocardiogram

There is no indication of a QT/QTc prolonging effect of SABRIL in single doses up to 6.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy subjects were administered a single oral dose of SABRIL (3 g and 6 g) and placebo. Peak concentrations for 6.0 g SABRIL were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

12.3 Pharmacokinetics

Vigabatrin displayed linear pharmacokinetics after administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g and 2.0 g twice daily with a half-life of about 7.5 hours. Bioequivalence has been established between the oral solution and tablet formulations.

Absorption

Following oral administration, vigabatrin is essentially completely absorbed. Time to maximum concentration (t_{max}) is approximately 1 hour following single and multiple doses. There was little accumulation with multiple dosing. A food effect study

involving administration of vigabatrin to healthy volunteers under fasting and fed conditions indicated that the C_{max} was decreased by 33%, t_{max} was increased to 2 hours, and AUC was unchanged under fed conditions [see DOSAGE AND ADMINISTRATION (2)].

Distribution

Vigabatrin does not bind to plasma proteins. Vigabatrin is widely distributed throughout the body; mean steady-state volume of distribution is 1.1 L/Kg (CV = 20%).

Metabolism and Elimination

Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. The half-life of vigabatrin is about 7.5 hours. Following administration of $^{[14]}$C-vigabatrin to healthy male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

Pharmacokinetics in Special Populations

Geriatric

The renal clearance of vigabatrin in healthy elderly patients (≥ 65 years of age) was 36% less than those in healthy younger patients. This finding is confirmed by an analysis of data from a controlled clinical trial.

Gender

No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.

Race

No specific study was conducted to investigate the effects of race on SABRIL pharmacokinetics. A cross study comparison between 23 Caucasian and 7 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that the AUC, C_{max}, and half-life were similar for the two populations. However, the mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4 .0 L/hr). Inter-subject variability in renal clearance was 20% in Caucasians and was 30% in Japanese.

Renal Impairment

Mean AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in patients with mild renal impairment (CLcr from >50-80 mL/min) in comparison to normal subjects.

Mean AUC increased by two-fold and the terminal half-life increased by two-fold in patients with moderate renal impairment (CLcr from >30-50 mL/min) in comparison to normal subjects.

Mean AUC increased by 4.5-fold and the terminal half-life increased by 3.5-fold in patients with severe renal impairment (CLcr from >10-30 mL/min) in comparison to normal subjects.

Dosage adjustment, including starting at a lower dose, is recommended for patients with any degree of renal impairment [see USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Hepatic Impairment
Vigabatrin is not significantly metabolized. The pharmacokinetics of vigabatrin in patients with impaired liver function have not been studied.

Drug Interactions

Phenytoin
A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies. *In vitro* drug metabolism studies indicate that decreased phenytoin concentrations upon addition of vigabatrin therapy are likely to be the result of induction of cytochrome P450 2C enzymes in some patients. Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated.

Other AEDs
When co-administered with vigabatrin, phenobarbital concentration (from phenobarbital or primidone) was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be clinically relevant. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

Clonazepam
In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

Alcohol
Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g twice daily) indicated that neither drug influences the pharmacokinetics of the other.

Oral Contraceptives
In a double-blind, placebo-controlled study using a combination oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel, vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. Based on this study, vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives. Additionally, no significant

difference in pharmacokinetic parameters (elimination half-life, AUC, C_{max}, apparent oral clearance, time to peak, and apparent volume of distribution) of vigabatrin were found after treatment with ethinyl estradiol and levonorgestrel.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Vigabatrin showed no carcinogenic potential in mouse or rat when given in the diet at doses up to 150 mg/kg/day for 18 months (mouse) or at doses up to 150 mg/kg/day for 2 years (rat). These doses are less than the maximum recommended human dose (MRHD) of 3 g/day on a mg/m^2 basis.

Vigabatrin was negative in *in vitro* (Ames, CHO/HGPRT mammalian cell forward gene mutation, chromosomal aberration in rat lymphocytes) and in *in vivo* (mouse bone marrow micronucleus) assays.

No adverse effects on male or female fertility were observed in rats at oral doses up to 150 mg/kg/day (approximately 1/2 the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Complex Partial Seizures in Adults

The effectiveness of SABRIL as adjunctive therapy in adult patients with CPS was established in two U.S. multicenter, double-blind, placebo-controlled, parallel-group clinical studies. A total of 357 adults (age 18 to 60 years) with CPS, with or without secondary generalization were enrolled (Studies 1 and 2). Patients were required to be on an adequate and stable dose of an anticonvulsant, and have a history of failure on an adequate regimen of carbamazepine or phenytoin. Patients had a history of about 8 seizures per month (median) for about 20 years (median) prior to entrance into the study. These studies were not capable by design of demonstrating direct superiority of SABRIL over any other anticonvulsant added to a regimen to which the patient had not adequately responded. Further, in these studies patients had previously been treated with a limited range of anticonvulsants.

The primary measure of efficacy was the patient's reduction in mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized at end of study compared to baseline.

Study 1

Study 1 (N=174) was a randomized, double-blind, placebo-controlled, dose-response study consisting of an 8-week baseline period followed by an 18-week treatment period. Patients were randomized to receive placebo or 1, 3, or 6 g/day vigabatrin administered twice daily. During the first 6 weeks following randomization, the dose was titrated upward beginning with 1 g/day and increasing

by 0.5 g/day on days 1 and 5 of each subsequent week in the 3 g/day and 6 g/day groups, until the assigned dose was reached.

Results for the primary measure of effectiveness, reduction in mean monthly frequency of Complex Partial Seizures, are shown in Table 4. The 3 g/day and 6 g/day dose groups were statistically significantly superior to placebo, but the 6 g/day dose was not superior to the 3 g/day dose.

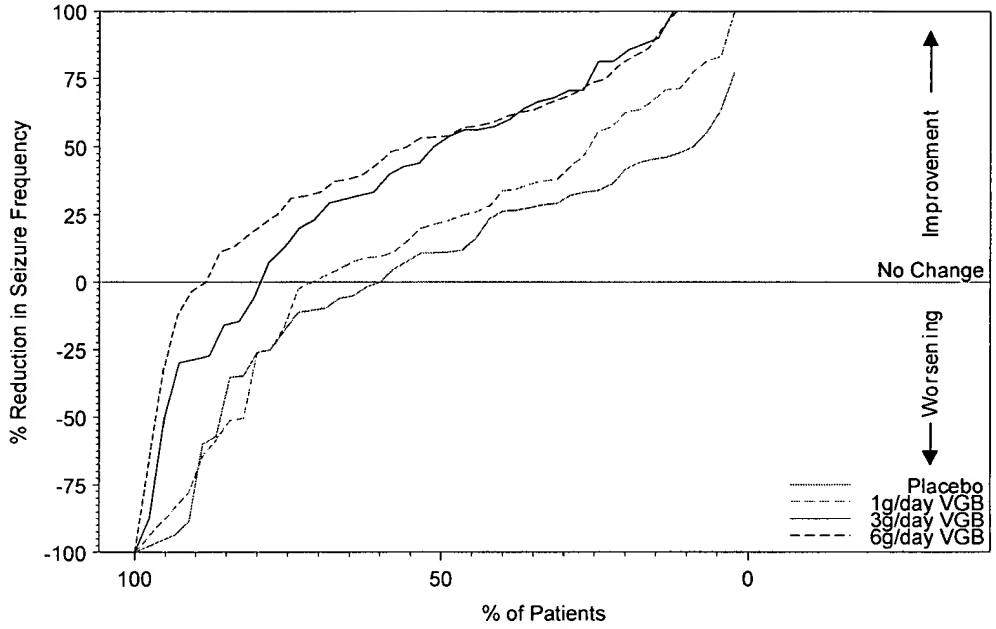
Table 4. Median Monthly Frequency of Complex Partial Seizures+

	N	Baseline	Endstudy
Placebo	45	9.0	8.8
1 g/day SABRIL	45	8.5	7.7
3 g/day SABRIL	41	8.5	3.7*
6 g/day SABRIL	43	8.5	4.5*

*P<0.05 compared to placebo
+Including one patient with simple partial seizures with secondary generalization only

Figure 1 presents the percentage of patients (X-axis) with a percent reduction in seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in complex partial seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in complex partial seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in complex partial seizure frequency was consistently higher for the SABRIL 3 and 6 g/day groups compared to the placebo group. For example, 51% of patients randomized to SABRIL 3 g/day and 53% of patients randomized to Sabril 6 g/day experienced a 50% or greater reduction in seizure frequency, compared to 9% of patients randomized to placebo. Patients with an increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

Figure 1. Percent Reduction from Baseline in Seizure Frequency



Study 2

Study 2 (N=183 randomized, 182 evaluated for efficacy) was a randomized, double-blind, placebo-controlled, parallel study consisting of an 8-week baseline period and a 16-week treatment period. During the first 4 weeks following randomization, the dose of vigabatrin was titrated upward beginning with 1 g/day and increased by 0.5 g/day on a weekly basis to the maintenance dose of 3 g/day.

Table 5. Median Monthly Frequency of Complex Partial Seizures

	N	Baseline	Endstudy
Placebo	90	9.0	7.5
3 g/day SABRIL	92	8.3	5.5*

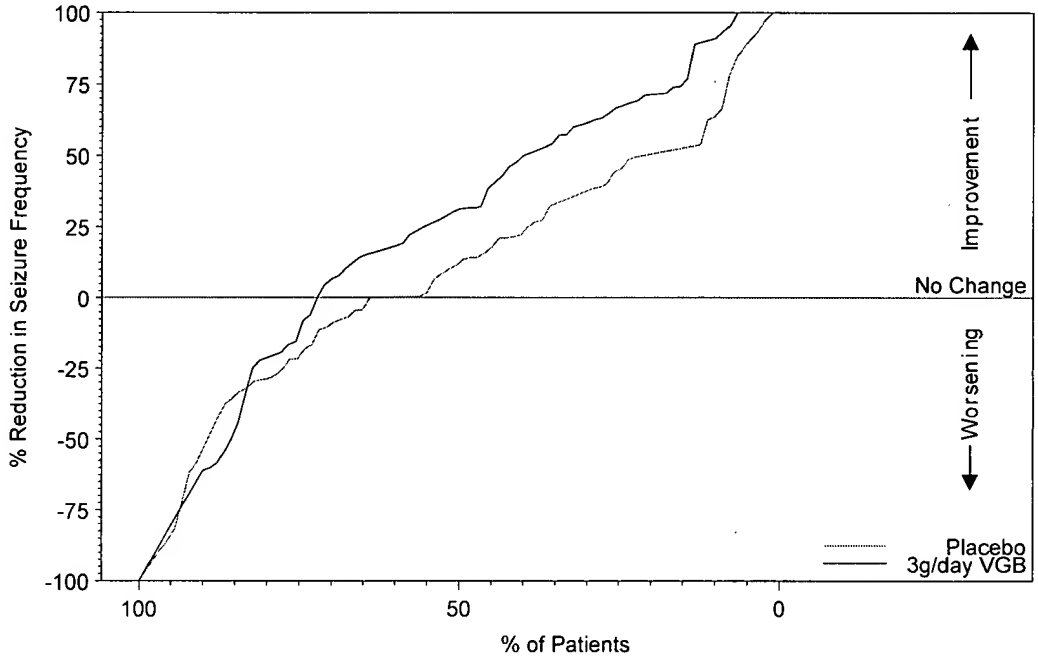
*P<0.05 compared to placebo

Results for the primary measure of effectiveness, reduction in mean monthly complex partial seizure frequency, are shown in Table 5. Vigabatrin 3 g/day was statistically significantly superior to placebo in reducing seizure frequency.

Figure 2 presents the percentage of patients (X-axis) with a percent reduction in seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in complex partial seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in complex partial seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure frequency was consistently higher for the SABRIL 3 g/day group compared to the placebo group. For example, 39% of patients randomized to SABRIL (3 g/day) experienced a

50% or greater reduction in complex partial seizure frequency, compared to 21% of patients randomized to placebo. Patients with an increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

Figure 2. Percent Reduction from Baseline in Seizure Frequency



For both studies, there was no difference in the effectiveness of vigabatrin between male and female patients. Analyses of age and race were not possible as nearly all patients were between the ages of 18 to 65 and Caucasian.

15 REFERENCES

None

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 SABRIL Tablet

Each SABRIL film-coated tablet contains 500 mg vigabatrin and is white, film-coated, oval, biconvex, scored on one side, and debossed with OV 111 on the other.

NDC 67386-111-01: Bottles of 100.

Store at 20-25°C (68-77°F). See USP controlled room temperature.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.5)

Patients must be informed of the availability of a Medication Guide. Patients must be instructed to read the Medication Guide prior to initiating treatment with SABRIL and with each prescription refill. Doctors must review the SABRIL Medication Guide with every patient prior to initiation of treatment. Patients should be instructed to take SABRIL only as prescribed.

17.1 Vision Loss

Patients should be informed of the risk of permanent vision loss, particularly loss of peripheral vision, from SABRIL, and the need for monitoring vision [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

Monitoring of vision, including assessment of visual fields and visual acuity, is required for adults at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy unless after repeated attempts it is not possible. In those patients in whom vision testing is not possible, treatment may continue according to clinical judgment with appropriate patient counseling and with documentation in the SHARE program of the inability to test vision. Patients should be informed that if baseline or subsequent vision is not normal, SABRIL should only be used if the benefits of SABRIL treatment clearly outweigh the risks of additional vision loss.

Patients should understand that vision testing may be insensitive and may not detect vision loss before it is severe. Patients should also understand that if vision loss is documented, such loss is irreversible.

Patients should be informed that if changes in vision are suspected, they should notify their physician immediately.

17.2 Suicidal Thinking and Behavior

Patients, their caregiver(s), and families should be counseled that AEDs, including SABRIL, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of concern should be reported immediately to healthcare providers [see WARNINGS AND PRECAUTIONS, Suicidal Behavior and Ideation (5.5)].

17.3 Use in Pregnancy

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1), and Nursing Mothers (8.2)].

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)]. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

17.4 Withdrawal of SABRIL Therapy

Patients should be told not to suddenly discontinue SABRIL therapy. As with all AEDs, withdrawal should be gradual. In controlled clinical studies in adults with CPS, vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued.

17.5 FDA-Approved Medication Guide

Manufactured by: Patheon
Cincinnati, OH 45237, U.S.A.

For: Lundbeck Inc.
Deerfield, IL 60015, U.S.A.

Issued: August 2009

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SABRIL safely and effectively. See full prescribing information for SABRIL.

Sabril® (vigabatrin) for Oral Solution
For Oral Administration Only
Initial U.S. Approval: 2009 **℞ Only**

WARNING: VISION LOSS
See full prescribing information for complete boxed warning

- SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity.
- Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss
- Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL
- Periodic vision testing is required for patients on SABRIL, but cannot reliably prevent vision damage
- Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program

----------INDICATIONS AND USAGE----------

SABRIL is an antiepileptic drug (AED) indicated for:

- **Infantile Spasms (IS) - 1 Month to 2 Years of Age** (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Infantile Spasms: Initiate therapy at 50 mg/kg/day twice daily increasing total daily dose per instructions to a maximum of 150 mg/kg/day (2.1)
- Dose adjustment recommended in renally impaired patients (2.2)
- Reduce dose gradually upon discontinuation (2.3)

----------DOSAGE FORM AND STRENGTHS----------

Powder for Oral Solution: 500 mg (3.1)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- SABRIL causes permanent vision loss (5.1)
- Abnormal MRI signal changes have been reported in some infants with IS receiving SABRIL (5.3)
- Antiepileptic drugs, including SABRIL, increase the risk of suicidal thoughts and behavior (5.5)
- Dose should be tapered gradually to avoid withdrawal seizures (5.6)
- SABRIL causes anemia (5.7)
- SABRIL causes somnolence and fatigue (5.8)
- SABRIL causes peripheral neuropathy (5.9)
- SABRIL causes weight gain (5.10)
- SABRIL causes edema (5.11)

----------ADVERSE REACTIONS----------

Most common adverse reactions described in adults (change of ≥5% over placebo) in addition to permanent vision loss in adult controlled trials with vigabatrin were fatigue, somnolence, nystagmus, tremor, vision blurred, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck Inc. at 1-800-455-1141 or www.lundbeckinc.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Decreased phenytoin plasma levels have been reported (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available (8.1)
- Nursing Mothers: SABRIL is excreted in human milk (8.2)
- Renal Impairment: Dose adjustment recommended (2.2, 8.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

Issued: 08/2009

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: VISION LOSS

- SABRIL causes permanent vision loss in infants, children and adults. Because assessing vision loss is difficult in children, the frequency and extent of vision loss in infants and children is poorly characterized. For this reason, the data described below is primarily based on the adult experience.
- In adults, SABRIL causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years.
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.
- It is possible that vision loss can worsen despite discontinuing SABRIL.
- Because of the risk of vision loss, SABRIL should be withdrawn from patients with infantile spasms who fail to show substantial clinical benefit within 2 to 4 weeks of initiation, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.
- In infants and children, vision loss may not be detected until it is severe. Nonetheless, vision should be assessed to the extent possible at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy. Once detected, vision loss due to SABRIL is not reversible. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.
- Symptoms of vision loss from SABRIL are unlikely to be recognized by the parent or caregiver before vision loss is severe. Vision loss of milder severity, although unrecognized by the caregiver, may still adversely affect function.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks
- The lowest dose and shortest exposure to SABRIL should be used that is consistent with clinical objectives
- The possibility that vision loss from SABRIL may be more common, more severe or have more severe functional consequences in infants and children than in adults cannot be excluded.

Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program called SHARE, by calling 1-888-45-SHARE. Only prescribers and pharmacies registered with SHARE may prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE [see WARNINGS AND PRECAUTIONS, Distribution Program for SABRIL (5.2)].

1 INDICATIONS AND USAGE

1.1 Infantile Spasms (1 Month to 2 Years of Age)

SABRIL® is indicated as monotherapy for pediatric patients with infantile spasms (IS) for whom the potential benefits outweigh the potential risk of vision loss [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Infantile Spasms (1 Month to 2 Years of Age)

Physicians should review and discuss the Medication Guide with the caregiver(s) prior to preparation and administration of SABRIL. Physicians should confirm that caregiver(s) understand how to reconstitute SABRIL and to administer the correct dose to their infants.

SABRIL should be given as twice daily oral administration with or without food. The initial dosing is 50 mg/kg/day given in two divided doses and can be titrated by 25-50 mg/kg/day increments every 3 days up to a maximum of 150 mg/kg/day [see USE IN SPECIFIC POPULATIONS, Pediatric Use (8.3)].

The entire contents of the appropriate number of packets (500 mg/packet) of powder should be emptied into an empty cup, and should be dissolved in 10 mL of cold or room temperature water per packet using the 10 mL oral syringe supplied with the medication. The concentration of the final solution is 50 mg/mL. Table 1 below describes how many packets and how many mL of water will be needed to prepare each individual dose. Each individual dose should be prepared immediately before use and administered cold or at room temperature.

Table 1. Number of Packages and mL of Water used for Each Individual Dose

Each Individual Dose (Prepared and Given Twice Daily)	Number of Packets	Number of mL of Water for Dissolving
0 to 500 mg	1 packet	10 mL
501 to 1000 mg	2 packets	20 mL
1001 to 1500 mg	3 packets	30 mL

Table 2 provides the volume that should be administered as individual doses in infants of various weights is presented below:

Table 2. Infant Dosing Table

Weight (kg)	Starting Dose 50 mg/kg/day	Maximum Dose 150 mg/kg/day
3	1.5 mL twice daily	4.5 mL twice daily
4	2 mL twice daily	6 mL twice daily
5	2.5 mL twice daily	7.5 mL twice daily
6	3 mL twice daily	9 mL twice daily
7	3.5 mL twice daily	10.5 mL twice daily

Table 2. Infant Dosing Table

8	4 mL twice daily	12 mL twice daily
9	4.5 mL twice daily	13.5 mL twice daily
10	5 mL twice daily	15 mL twice daily
11	5.5 mL twice daily	16.5 mL twice daily
12	6 mL twice daily	18 mL twice daily
13	6.5 mL twice daily	19.5 mL twice daily
14	7 mL twice daily	21 mL twice daily
15	7.5 mL twice daily	22.5 mL twice daily
16	8 mL twice daily	24 mL twice daily

2.2 Patients with Renal Impairment

SABRIL is primarily eliminated through the kidney. Information about how to adjust the dose in pediatric patients with renal impairment is unavailable.

The following dose adjustments are pertinent to the possible use of this dosage form in adults with renal impairment:

In patients with mild renal impairment (CLcr >50 to 80 mL/min), the dose should be decreased by 25%; in patients with moderate renal impairment (CLcr >30 to 50 mL/min), the dose should be decreased by 50%; and in patients with severe renal impairment (CLcr >10 to <30 mL/min), the dose should be decreased by 75%.

CLcr in mL/min may be estimated from a serum creatinine (mg/dL) determination using the following formula:

CLcr *= [140-*age* (*years*)] *weight* (*kg*)/72 *serum creatinine* (*mg/dL*)]
*[0.85 *for female patients*]

The effect of dialysis on SABRIL clearance has not been adequately studied.

[see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5)].

2.3 General Dosing Considerations

Monitoring of SABRIL plasma concentrations to optimize therapy is not helpful. If a decision is made to discontinue SABRIL, the dose should be gradually reduced. In a controlled clinical study in patients with IS, vigabatrin was tapered by decreasing the dose at a rate of 25-50 mg/kg every 3-4 days [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6)].

3 DOSAGE FORMS AND STRENGTHS

3.1 Powder for Oral Solution

500 mg Packet.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Vision Loss (see BOXED WARNING)

Because of the risk of vision loss and because SABRIL, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 2 to 4 weeks of initiation of treatment, should be withdrawn from SABRIL. If in the clinical judgment of the prescriber evidence of treatment failure becomes obvious earlier than 2 to 4 weeks, treatment with SABRIL should be discontinued at that time. Patient response to and continued need for treatment should be periodically assessed.

Monitoring of Vision

Because vision testing in infants and children is difficult, vision loss may not be detected until it is severe. However, monitoring of vision by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina, must be performed at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. This assessment should include visual acuity and visual field whenever possible.

The diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor vision periodically must be documented under the SHARE program. In patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate caregiver(s) counseling, and with documentation in the SHARE program of the inability to test vision. Because of variability, results from ophthalmic monitoring must be interpreted with caution, and repeat testing is recommended if results are abnormal or uninterpretable.

The onset and progression of vision loss from SABRIL is unpredictable, and may occur or worsen precipitously. Once detected, vision loss due to SABRIL is not reversible.

5.2 Distribution Program for SABRIL

SABRIL is available only under a special restricted distribution program called the SHARE program. Under the SHARE program, only prescribers and pharmacies registered with the program are able to prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE. Contact the SHARE program at 1-888-45-SHARE.

To enroll in SHARE, prescribers must understand the risks of SABRIL and complete the SHARE Prescriber Enrollment and Agreement Form indicating agreement to:

- Enroll all patients in SHARE
- Review the SABRIL Medication Guide with every caregiver
- Educate caregiver(s) on the risks of SABRIL, including the risk of vision loss [see BOXED WARNING: VISION LOSS]
- Arrange for visual field and retinal exam by an expert examiner and review visual evaluation prior to initiation of SABRIL treatment and every 3 months during therapy
- Remove patients from SABRIL therapy if the patients do not experience a meaningful reduction in seizures
- Counsel caregiver(s) who fail to comply with the program requirements
- Remove patients from SABRIL therapy whose caregiver(s) fail to comply with the program requirements after appropriate counseling

5.3 Magnetic Resonance Imaging (MRI) Abnormalities

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with SABRIL. In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 21.5% in SABRIL treated patients versus 4.1% in patients treated with other therapies.

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment. In a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied.

Neurotoxicity (including convulsions and hypomyelination) was observed in rats exposed to vigabatrin during late gestation and the neonatal and juvenile periods of development. The relationship between these findings and the abnormal MRI findings in infants treated for IS with vigabatrin is unknown [see WARNINGS AND PRECAUTIONS, Neurotoxicity (5.4) and USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)].

The specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with vigabatrin for refractory complex partial seizures (CPS). In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo patients.

5.4 Neurotoxicity

Vacuolization, characterized by fluid accumulation and separation of the outer layers of myelin, has been observed in brain white matter tracts in adult and juvenile rats and adult mice, dogs, and possibly monkeys following administration of vigabatrin. This lesion, referred to as intramyelinic edema (IME), was seen in animals at doses within the human therapeutic range. A no-effect dose was not established in rodents or dogs. In the rat and dog, vacuolization was reversible following discontinuation of vigabatrin treatment, but, in the rat, pathologic changes consisting of swollen or degenerating axons, mineralization, and gliosis were seen in brain areas in which vacuolation had been previously observed. Vacuolization in adult animals was correlated with alterations in MRI and changes in visual and somatosensory evoked potentials (EP).

Administration of vigabatrin to rats during the neonatal and juvenile periods of development produced vacuolar changes in the gray matter (areas including the thalamus, midbrain, deep cerebellar nuclei, substantia nigra, hippocampus, and forebrain) which are considered distinct from the IME observed in vigabatrin treated adult animals. Decreased myelination, retinal dysplasia, and neurobehavioral abnormalities (convulsions, neuromotor impairment, learning deficits) were also observed following vigabatrin treatment of young rats. These effects occurred at doses associated with plasma vigabatrin levels substantially lower than those achieved clinically in infants and children.

In a published study, vigabatrin (200, 400 mg/kg/day) induced apoptotic neurodegeneration in the brain of young rats when administered by intraperitoneal injection on postnatal days 5-7.

Administration of vigabatrin to female rats during pregnancy and lactation at doses below those used clinically resulted in hippocampal vacuolation and convulsions in the mature offspring.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3)].

5.5 Suicidal Behavior and Ideation

The following information is pertinent to the possible use of this dosage form in adults. Antiepileptic drugs (AEDs), including SABRIL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing SABRIL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregiver(s), and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert

for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, SABRIL should be withdrawn gradually.

Caregivers should be told not to suddenly discontinue SABRIL therapy. In a controlled clinical study in patients with IS, vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days [see DOSAGE AND ADMINISTRATION, General Dosing Considerations (2.3), PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.5)].

5.7 Anemia

In North American controlled trials in adults, 5.7% of patients (16/280) receiving SABRIL and 1.6% of patients (3/188) receiving placebo had adverse events of anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled trials, there were mean decreases in hemoglobin of about 3% and 0% in SABRIL and placebo-treated patients, respectively, and in hematocrit of about 1% in Sabril treated patients compared to a gain of about 1% in patients treated with placebo.

In controlled and open label epilepsy trials in adults and pediatric patients, 3 SABRIL patients (0.06%, 3/4855) discontinued for anemia and 2 SABRIL patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or hematocrit below 24%.

5.8 Somnolence and Fatigue

SABRIL causes somnolence and fatigue. Patients should be advised not to drive a car or operate other complex machinery until they are familiar with the effects of SABRIL on their ability to perform such activities.

Pooled data from two SABRIL controlled trials in adults demonstrated that 24% (54/222) of SABRIL patients experienced somnolence compared to 10% (14/135) of placebo patients. In those same studies, 28% of SABRIL patients experienced fatigue compared to 15% (20/135) of placebo patients. Almost 1% of SABRIL patients discontinued from clinical trials for somnolence and almost 1% discontinued for fatigue.

5.9 Peripheral Neuropathy

SABRIL has been shown to cause symptoms of peripheral neuropathy in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not these symptoms occur in the pediatric population.

In a pool of North American controlled and uncontrolled epilepsy studies, 4.2% (19/457) of SABRIL treated patients developed signs and/or symptoms of peripheral neuropathy. In the subset of North American placebo controlled epilepsy trials, 1.4% (4/280) of SABRIL treated patients and no (0/188) placebo patients developed signs and/or symptoms of peripheral neuropathy. Initial manifestations of peripheral neuropathy in these trials included, in some combination, symptoms of numbness or tingling in the toes or feet, signs of reduced distal lower limb vibration or position sensation, or progressive loss of reflexes, starting at the ankles. Clinical studies in the development program were not designed to investigate peripheral neuropathy systematically and did not include nerve conduction studies, quantitative sensory testing, or skin or nerve biopsy. There is insufficient evidence to determine if development of these signs and symptoms were related to duration of SABRIL treatment, cumulative dose, or if the findings of peripheral neuropathy were completely reversible upon discontinuation of SABRIL.

5.10 Weight Gain

SABRIL has been shown to cause weight gain in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not weight gain occurs in the pediatric population.

Data pooled from randomized controlled trials found that 17% (77/443) of SABRIL patients gained ≥ 7% of baseline body weight versus 8% (22/275) of placebo patients. In these same trials, the mean weight change among SABRIL patients was 3.5 kg compared to 1.6 kg for placebo patients. In all epilepsy trials, 0.6% (31/4855) of SABRIL patients discontinued for weight gain. The long term effects of SABRIL related weight gain are not known. Weight gain was not related to the occurrence of edema.

5.11 Edema

SABRIL has been shown to cause edema in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not edema occurs in the pediatric population.

Pooled data from controlled trials demonstrated increased risk among SABRIL patients compared to placebo patients for peripheral edema (SABRIL 2%, placebo 1%), and edema (SABRIL 1%, placebo 0%). In these studies, one SABRIL and no placebo patients discontinued for an edema related AE. There was no apparent association between edema and cardiovascular adverse events such as hypertension or congestive heart failure. Edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

6 ADVERSE REACTIONS

SABRIL causes permanent damage to vision in a high percentage of patients [see BOXED WARNING: VISION LOSS and WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Events in U.S. and Primary Non-U.S. Clinical Studies

In U.S. and primary non-U.S. clinical studies of 3139 adult and 999 pediatric patients treated with SABRIL, the most commonly observed (≥ 5%) adverse events associated with the use of SABRIL in combination with other AEDs were headache (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsion (11%), nasopharyngitis (10%), weight increased (10%), upper respiratory tract infection (10%), visual field defect (9%), depression (8%), tremor (7%), nystagmus (7%), nausea (7%), diarrhea (7%), memory impairment (7%), insomnia (7%), irritability (7%), coordination abnormal (7%), vision blurred (6%), diplopia (6%), vomiting (6%), influenza (6%), pyrexia (6%), and rash (6%).

The adverse reactions most commonly associated with SABRIL treatment discontinuation in ≥ 1% of IS patients were infections (1.5%), status epilepticus (1.2%), developmental coordination disorder (1.2%), dystonia (1.2%), hypotonia (1.2%), hypertonia (1.2%), weight increased (1.2%), and insomnia (1.2%).

Most Common Adverse Reactions in Controlled Clinical Trials

Infantile Spasms

In a randomized, placebo-controlled IS study with a 5 day double-blind treatment phase (n=40), the adverse events reported by >5% of SABRIL patients and that occurred more frequently than in placebo patients were somnolence (SABRIL 45%, placebo 30%), bronchitis (SABRIL 30%, placebo 15%), ear infection (SABRIL 10%, placebo 5%), and otitis media acute (SABRIL 10%, placebo 0).

In a dose response study of low-dose (18-36 mg/kg/day) versus high-dose (100-148 mg/kg/day) vigabatrin, no clear correlation between dose and incidence of adverse events was observed. The treatment emergent adverse reactions (≥ 5% in either dose group) are summarized in Table 4.

Table 4. Treatment Emergent Adverse Events Occurring in ≥5% of Patients (Study 1A)

Body System Event	SABRIL Low Dose [N = 114] %	SABRIL High Dose [N = 108] %
Eye Disorders (other than field or acuity changes)		
Strabismus	5	5
Conjunctivitis	5	2
Gastrointestinal Disorders		
Vomiting	14	20
Constipation	14	12
Diarrhea	13	12
General Disorders		
Fever	29	19
Infections		
Upper respiratory tract infection	51	46
Otitis media	44	30
Viral infection	20	19
Pneumonia	13	11
Candidiasis	8	3
Ear infection	7	14
Gastroenteritis viral	6	5
Sinusitis	5	9
Urinary tract infection	5	6
Influenza	5	3
Croup infectious	5	1
Metabolism & Nutrition Disorders		
Decreased appetite	9	7
Nervous System Disorders		
Sedation	19	17
Somnolence	17	19
Status epilepticus	6	4
Lethargy	5	7
Convulsion	4	7
Hypotonia	4	6
Psychiatric Disorders		
Irritability	16	23
Insomnia	10	12
Respiratory Disorders		
Nasal congestion	13	4
Cough	3	8
Skin & Subcutaneous Tissue Disorders		
Rash	8	11

Refractory Complex Partial Seizures in Adults

Because controlled trials in infants were of short duration and enrolled few patients, the adverse events from clinical trials in adults are presented. Table 5 lists the treatment emergent adverse reactions that occurred in ≥2% of SABRIL patients and that occurred more frequently than in placebo patients from 2 U.S. add-on clinical studies of refractory complex partial seizures in adults.

Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
Eye Disorders		
Vision blurred	11	5
Diplopia	3	0
Eye disorder (other than field or acuity changes)	3	0
Asthenopia	2	0
Gastrointestinal Disorders		
Diarrhea	10	7
Nausea	9	8
Vomiting	7	6
Constipation	6	3
Abdominal pain upper	5	2
Dyspepsia	4	3
Stomach discomfort	3	1
Hemorrhoids	2	0
General Disorders		
Fatigue	27	16
Asthenia	5	2
Peripheral edema	5	1
Fever	5	3
Infections		
Nasopharyngitis	13	10
Upper respiratory tract infection	9	5
Influenza	5	4
Urinary tract infection	4	0
Injury		
Contusion	4	2
Metabolism and Nutritional Disorders		
Fluid retention	2	0
Increased appetite	2	0
Weight increased	8	3
Musculoskeletal Disorders		
Arthralgia	8	3
Back pain	6	2
Pain in extremity	5	4
Myalgia	3	2
Joint swelling	2	0
Muscle spasms	2	1
Shoulder pain	2	1
Nervous System Disorders		
Somnolence	22	13
Dizziness	21	17
Nystagmus	15	9
Tremor	14	8
Memory impairment	10	3
Coordination abnormal	9	2
Disturbance in attention	5	1
Sensory disturbance	5	2
Hyporeflexia	5	1
Parasthesia	5	1

Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
Lethargy	4	2
Hypoaesthesia	3	2
Sedation	2	0
Status epilepticus	2	0
Dysarthria	2	1
Psychiatric Disorders		
Irritability	10	7
Depression	7	3
Confusional state	6	1
Depressed mood	4	1
Anxiety	4	3
Thinking abnormal	3	0
Abnormal behavior	3	1
Aggression	2	0
Reproductive System		
Dysmenorrhea	7	3
Respiratory and Thoracic Disorders		
Pharyngolaryngeal pain	9	5
Dyspnea	2	0
Sinus headache	4	1

6.2 Post Marketing Experience

The following serious adverse events have been reported since approval and use of SABRIL worldwide. All serious adverse events that are not listed above as adverse events reported in clinical trials, that are not relatively common in the population and are not too vague to be useful are listed in this section. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Events are categorized by system organ class.

Birth Defects: Congenital cardiac defects, congenital external ear anomaly, congenital hemangioma, congenital hydronephrosis, congenital male genital malformation, congenital oral malformation, congenital vesicoureteric reflux, dentofacial anomaly, dysmorphism, fetal anticonvulsant syndrome, hamartomas, hip dysplasia, limb malformation, limb reduction defect, low set ears, renal aplasia, retinitis pigmentosa, supernumerary nipple, talipes

Ear: Deafness

Endocrine: Delayed puberty

Gastrointestinal: Gastrointestinal hemorrhage, esophagitis

General: Developmental delay, facial edema, malignant hyperthermia, multi-organ failure

Hepatobiliary: Cholestasis

Nervous System: Dystonia, encephalopathy, hypertonia, hypotonia, muscle spasticity, myoclonus, optic neuritis

Psychiatric: Acute psychosis, apathy, delirium, hypomania, neonatal agitation, psychotic disorder

Respiratory: Laryngeal edema, pulmonary embolism, respiratory failure, stridor

Skin and Subcutaneous Tissue: Angioedema, maculo-papular rash, pruritus

7 DRUG INTERACTIONS

For detailed information about Drug Interactions see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions (12.3).

7.1 Phenytoin

A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies.

7.2 Other AEDs

There are no clinically significant pharmacokinetics interactions between SABRIL and either phenobarbital or sodium valproate. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

7.3 Clonazepam

In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

7.4 Oral Contraceptives

SABRIL is unlikely to affect the efficacy of steroid oral contraceptives.

7.5 Drug-Laboratory Test Interactions

SABRIL decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. In some patients, these enzymes become undetectable. The suppression of ALT and AST activity by SABRIL may preclude the use of these markers, especially ALT, to detect early hepatic injury.

SABRIL may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The following information is pertinent to the possible use of this dosage form in adults.

Pregnancy Category C. Vigabatrin produced developmental toxicity, including teratogenic and neurohistopathological effects, when administered to pregnant animals at clinically relevant doses. In addition, developmental neurotoxicity was observed in rats treated with vigabatrin during a period of postnatal development corresponding to the third trimester of human pregnancy. There are no adequate and well-controlled studies in pregnant women. SABRIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of vigabatrin (oral doses of 50 to 200 mg/kg) to pregnant rabbits throughout the period of organogenesis was associated with an increased incidence of malformations (cleft palate) and embryo-fetal death; these findings were observed in two separate studies. The no-effect dose for teratogenicity and embryolethality in rabbits (100 mg/kg) is approximately 1/2 the maximum recommended human dose (MRHD) of 3 g/day on a body surface area (mg/m^2) basis for adults treated for refractory complex partial seizures with vigabatrin. In rats, oral administration of vigabatrin (50, 100, or 150 mg/kg) throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal anatomic variations. The no-effect dose for embryo-fetal toxicity in rats (50 mg/kg) is approximately 1/5 the MRHD in adults on a mg/m^2 basis. Oral administration of vigabatrin (50, 100, 150 mg/kg) to rats from the latter part of pregnancy through weaning produced long-term neurohistopathological (hippocampal vacuolation) and neurobehavioral (convulsions) abnormalities in the offspring. A no-effect dose for developmental neurotoxicity in rats was not established; the low-effect dose (50 mg/kg) is approximately 1/5 the MRHD in adults on a mg/m^2 basis.

In a published study, vigabatrin (300 or 450 mg/kg) was administered by intraperitoneal injection to a mutant mouse strain on a single day during organogenesis (day 7, 8, 9, 10, 11, or 12). An increase in malformations (including cleft palate) was observed at both doses.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The early postnatal period in rats is

generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to SABRIL, physicians are advised to recommend that pregnant patients taking SABRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.2 Nursing Mothers

The following information is pertinent to the possible use of this dosage form in adults.

Vigabatrin is excreted in human milk. Because of the potential for serious adverse reactions from vigabatrin in nursing infants [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

SABRIL is indicated as monotherapy for pediatric patients with IS (1 month to 2 years of age) for whom the potential benefits outweigh the potential risk for developing permanent vision loss.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 21.5% in vigabatrin treated patients versus 4.1% in patients treated with other therapies. A dose-dependent relationship may exist, as children with IS who were exposed to a higher vigabatrin dose (≥125 mg/kg/day) had a prevalence of 29.5%, while those exposed to lower doses of vigabatrin had a prevalence of 12.5%; however, these differences were not statistically significant (p=0.099).

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment, although in a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)].

The specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with vigabatrin for refractory CPS. In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo patients.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

8.4 Geriatric Use

The following information is pertinent to the possible use of this dosage form in adults.

Clinical studies of vigabatrin did not include sufficient numbers of patients aged 65 and over to determine whether they responded differently from younger patients.

Vigabatrin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Oral administration of a single dose of 1.5 g of vigabatrin to elderly (>65 years) patients with reduced creatinine clearance (<50 mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days. The renal clearance of vigabatrin was 36% lower in healthy elderly subjects (>65 years) than in young healthy males. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.5 Renal Impairment

Information about how to adjust the dose in pediatric patients with renal impairment is unavailable.

The following dose adjustments are pertinent to the possible use of this dosage form in adults with renal impairment:

In adults, dose adjustment, including initiating treatment with a lower dose, is necessary in patients with mild (creatinine clearance >50-80 mL/min), moderate (creatinine clearance >30-50 mL/min) and severe (creatinine clearance >10-30 mL/min) renal impairment [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Class
Vigabatrin is not a controlled substance.

9.2 Abuse
Vigabatrin did not produce adverse events or overt behaviors associated with abuse when administered to humans or animals. It is not possible to predict the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking behavior).

9.3 Dependence
Following chronic administration of vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, vigabatrin should be withdrawn gradually to minimize increased seizure frequency [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6) and PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.5)].

10 OVERDOSAGE

10.1 Signs, Symptoms, and Laboratory Findings of Overdosage
Confirmed and/or suspected vigabatrin overdoses have been reported during clinical studies and in post marketing surveillance. No vigabatrin overdoses resulted in death. When reported, the vigabatrin dose ingested ranged from 3 g to 90 g, but most were between 7.5 g and 30 g. Nearly half the cases involved multiple drug ingestions including carbamazepine, barbiturates, benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine.

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of vigabatrin overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability,

confusion, headache, hypotension, abnormal behavior, increased seizure activity, status epilepticus, and speech disorder. These symptoms resolved with supportive care.

10.2 Treatment or Management for Overdosage

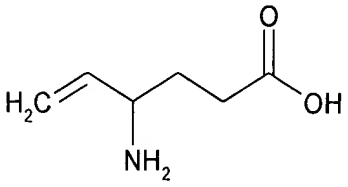
There is no specific antidote for SABRIL overdose. Standard measures to remove unabsorbed drug should be used, including elimination by emesis or gastric lavage. Supportive measures should be employed, including monitoring of vital signs and observation of the clinical status of the patients.

In an *in vitro* study, activated charcoal did not significantly adsorb vigabatrin.

The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

11 DESCRIPTION

Table 6. Description

Proprietary Name:	SABRIL®
Established Name:	Vigabatrin for Oral Solution
Dosage Form:	Packet
Route of Administration:	Oral
Pharmacologic Class of Drug:	Antiepileptic
Chemical Name:	(±) 4-amino-5-hexenoic acid
Structural Formula:	

SABRIL (vigabatrin) is available as a white granular powder for oral administration. Each packet contains 500 mg vigabatrin. Each packet also contains the inactive ingredient povidone. Vigabatrin is an oral antiepileptic drug with the chemical name (±) 4-amino-5-hexenoic acid. It is a racemate consisting of two enantiomers. The molecular formula is $C_6H_{11}NO_2$ and the molecular weight is 129.16.

Vigabatrin is a white to off-white powder which is freely soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n-octanol/water partition coefficient of vigabatrin is about 0.011 (log *P*=-1.96) at physiologic pH. Vigabatrin melts with decomposition in a 3-degree range within the temperature interval of 171°C to 176°C. The dissociation constants (pK_a) of vigabatrin are 4 and 9.7 at room temperature (25°C).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the central nervous system.

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

12.2 Pharmacodynamics

Effects on Electrocardiogram

There is no indication of a QT/QTc prolonging effect of SABRIL in single doses up to 6.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy adult subjects were administered a single oral dose of SABRIL (3 g and 6 g) and placebo. Peak concentrations for 6.0 g SABRIL were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

12.3 Pharmacokinetics

Vigabatrin displayed linear pharmacokinetics after administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g to 2.0 g twice daily. Bioequivalence has been established between the oral solution and tablet formulations.

Absorption

Following oral administration, vigabatrin is essentially completely absorbed.
Time to maximum concentration (t_{max}) is approximately 2.5 hours in infants and about 1 hour in children following a single dose. There was little accumulation with multiple dosing. A food effect study involving administration of vigabatrin to healthy adult volunteers under fasting and fed conditions indicated that the C_{max} was decreased by 33%, t_{max} increased to 2 hours, and AUC was unchanged under fed conditions [see DOSAGE AND ADMINISTRATION, Infantile Spasms (2.1)].

Distribution
Vigabatrin does not bind to plasma proteins. Vigabatrin is widely distributed throughout the body; mean steady-state volume of distribution is 1.1 L/Kg (CV = 20%).

Metabolism and Elimination
Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. The half-life of vigabatrin in adults is about 7.5 hours and about 5.7 hours in infants. Following administration of $^{[14]}$C-vigabatrin to healthy adult male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

Pharmacokinetics in Special Populations

Geriatric
The renal clearance of vigabatrin in healthy elderly patients (≥ 65 years of age) was 36% less than those in healthy younger patients. A population PK analysis of patient data also confirmed these differences in age.

Pediatric
The clearance of infants and children were 2.4±0.8 and 5.7±2.5 L/h, respectively compared to 7 L/h in adults.

Gender
No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.

Race
No specific study was conducted to investigate the effects of race on SABRIL pharmacokinetics. A cross study comparison in adults between 23 Caucasian and 7 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that the AUC, $C_{max,}$ and half-life were similar for the two populations. However, the mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4.0 L/hr). Inter-subject variability in renal clearance was 20% in Caucasians and was 30% in Japanese.

Renal Impairment
There is no information available about the pharmacokinetics of vigabatrin in pediatric patients with renal impairment.

In adult patients with mild renal impairment (CLcr from >50-80 mL/min), mean AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in comparison to the normal subjects. Mean AUC increased by two-fold and the terminal half-life increased by two-fold in patients with moderate renal impairment (CLcr from >30-50 mL/min) in comparison to the normal subjects. Mean AUC

increased by 4.5-fold and the terminal half-life increased by 3.5-fold in patients with severe renal impairment (CLcr from >10-30 mL/min) in comparison to the normal subjects.

While dose adjustments are warranted in renally impaired pediatric patients, no data is available to guide dose adjustments in this patient population. Dosage adjustment in adults with renal impairment is recommended [see USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Hepatic Impairment
Vigabatrin is not significantly metabolized. The pharmacokinetics of vigabatrin in patients with impaired liver function have not been studied.

Drug Interactions

Phenytoin
A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies. *In vitro* drug metabolism studies indicate that decreased phenytoin concentrations upon addition of vigabatrin therapy are likely due to induction of cytochrome P450 2C enzymes in some patients. Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated.

Other AEDs
When co-administered with vigabatrin, phenobarbital concentration (from phenobarbital or primidone) was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be clinically relevant. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

Clonazepam
In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

Alcohol
Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g twice daily) indicated that neither drug influences the pharmacokinetics of the other.

Oral Contraceptives
In a double-blind, placebo-controlled study using a combination oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel, vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. Based on this study, vigabatrin is unlikely to

affect the efficacy of steroid oral contraceptives. Additionally, no significant difference in pharmacokinetic parameters (elimination half–life, AUC, C_{max}, apparent oral clearance, time to peak, and apparent volume of distribution) of vigabatrin were found after treatment with ethinyl estradiol and levonorgestrel.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Vigabatrin showed no carcinogenic potential in mouse or rat when given in the diet at doses up to 150 mg/kg/day for 18 months (mouse) or at doses up to 150 mg/kg/day for 2 years (rat). These doses are less than the maximum recommended human dose (MRHD) for IS (150 mg/kg/day) and for refractory complex partial seizures in adults (3 g/day) on a mg/m^2 basis.

Vigabatrin was negative in *in vitro* (Ames, CHO/HGPRT mammalian cell forward gene mutation, chromosomal aberration assay in rat lymphocytes) and in *in vivo* (mouse bone marrow micronucleus) assays.

No adverse effects on male or female fertility were observed in rats at oral doses up to 150 mg/kg/day (approximately 1/2 the MRHD of 3 g/day (on a mg/m^2 basis) for adults treated for refractory complex partial seizures with vigabatrin.

14 CLINICAL STUDIES

14.1 Infantile Spasms

The effectiveness of SABRIL as monotherapy was established for IS in two multicenter controlled studies. Both studies were similar in terms of disease characteristics and prior treatments of patients and all enrolled infants had a confirmed diagnosis of IS.

Study 1

Study 1 (N=221) was a multicenter, randomized, low-dose high-dose, parallel group, partially-blinded (caregivers knew the actual dose but not whether their child was classified as low or high dose; EEG reader was blinded but investigators were not blinded) study to evaluate the safety and efficacy of vigabatrin in patients <2 years of age with new-onset Infantile Spasms. Patients with both symptomatic and cryptogenic etiologies were studied. The study was comprised of two phases. The first phase was a 14 to 21 day partially-blind phase in which patients were randomized to receive either low- dose (18-36 mg/kg/day) or high-dose (100-148 mg/kg/day) vigabatrin. Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the patient became spasm-free on or before day 14, another 7 days of constant dose was administered. The primary efficacy endpoint of this study was the proportion of patients who were spasm-free for 7 consecutive days beginning within the first 14 days of vigabatrin therapy. Patients considered

spasm-free were defined as those patients who remained free of spasms (evaluated according to caregiver response to direct questioning regarding spasm frequency) and who had no indication of spasms or hypsarrhythmia during 8 hours of CCTV EEG recording (including at least one sleep-wake-sleep cycle) performed within 3 days of the seventh day of spasm freedom and interpreted by a blinded EEG reader. Seventeen patients in the high dose group achieved spasm freedom compared with 8 patients in the low dose group. This difference was statistically significant (p=0.0375). Primary efficacy results are shown in Table 7.

Table 7. Spasm Freedom by Primary Criteria (Study 1A)

	SABRIL Treatment Group	
	18-36 mg/kg/day [N=114] n (%)	100-148 mg/kg/day [N=107] n (%)
Patients who Achieved Spasm Freedom	8 (7.0)	17 (15.9)

p=0.0375

Note: Primary criteria were evaluated based on caregiver assessment plus CCTV EEG confirmation within 3 days of the seventh day of spasm freedom.

Study 2

Study 2 (N=40) was a multicenter, randomized, double-blind, placebo-controlled, parallel group study consisting of a pre-treatment (baseline) period of 2-3 days, followed by a 5-day double-blind treatment phase during which patients were treated with vigabatrin (initial dose of 50 mg/kg/day with titration allowed to 150 mg/kg/day) or placebo. The primary efficacy endpoint in this study was the average percent change in daily spasm frequency, assessed during a pre-defined and consistent 2-hour window of evaluation, comparing baseline to the final 2 days of the 5-day double-blind treatment phase. No statistically significant differences were observed in the average frequency of spasms using the 2-hour evaluation window. However, a post-hoc alternative efficacy analysis, using a 24-hour clinical evaluation window found a statistically significant difference in the overall percentage of reductions in spasms between the vigabatrin group (68.9%) and the placebo group (17.0%) (p=0.030).

15 REFERENCES

None

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 SABRIL Packet

Each SABRIL packet contains 500 mg vigabatrin as a white to off-white granular powder.

NDC 67386-211-65: Packages of 50.

Store at 20-25°C (68-77°F). See USP controlled room temperature.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.6)

Caregivers must be informed of the availability of a Medication Guide. They must be instructed to read the Medication Guide prior to initiating treatment with SABRIL and with each prescription refill. Doctors must review the SABRIL Medication Guide with every caregiver prior to initiation of treatment. Caregivers should be instructed to administer SABRIL only as prescribed.

Physicians should confirm that caregiver(s) understand how to reconstitute SABRIL for Oral Solution and to administer the correct dose to their infants.

17.1 Vision Loss

Caregiver(s) should be informed of the risk of permanent vision loss, particularly loss of peripheral vision, from SABRIL, and the need for monitoring vision [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

Although vision testing in infants is insensitive, vision must be assessed to the extent possible at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy. Caregiver(s) should understand that vision testing is insensitive in infants and may not detect vision loss before it is severe. Caregiver(s) should also understand that if vision loss is documented, such loss is irreversible [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

Caregiver(s) should be informed that if changes in vision are suspected, they should notify their physician immediately.

17.2 MRI Abnormalities

Caregiver should be informed of the possibility of developing abnormal MRI signal changes of unknown clinical significance.

17.3 Suicidal Thinking and Behavior

The following information is pertinent to the possible use of this dosage form in adults.

Patients, their caregiver(s), and families should be counseled that AEDs, including SABRIL, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of concern should be reported immediately to healthcare providers [see WARNINGS AND PRECAUTIONS, Suicidal Behavior and Ideation (5.5)].

17.4 Use in Pregnancy

The following information is pertinent to the possible use of this dosage form in adults.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1), Nursing Mothers (8.2)].

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)]. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

17.5 Withdrawal of SABRIL Therapy

Caregiver(s) should be told not to suddenly discontinue SABRIL therapy in their infant. As with all AEDs, withdrawal should be gradual. In a controlled clinical study in patients with IS, vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days.

17.6 FDA-Approved Medication Guide

Manufactured by: Patheon
Cincinnati, OH 45237, U.S.A.

For: Lundbeck Inc.
Deerfield, IL 60015, U.S.A.

Issued: August 2009

Attachment D

[US Patent 5,380,936]

US005380936A

United States Patent [19]

Casara

[11] Patent Number: 5,380,936

[45] Date of Patent: Jan. 10, 1995

[54] **PROCESS FOR PREPARING 4-AMINO-5-HEXENOIC ACID**

[75] Inventor: **Patrick Casara**, Ittenheim, France

[73] Assignee: **Merrell Dow Pharmaceuticals Inc.**, Cincinnati, Ohio

[21] Appl. No.: **184,762**

[22] Filed: **Jan. 19, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 986,636, Dec. 7, 1992, abandoned.

[30] **Foreign Application Priority Data**

Dec. 10, 1991 [EP] European Pat. Off. 91403351.9

[51] **Int. Cl.**[6] **C07C 229/00**

[52] **U.S. Cl.** **562/574**; 558/6; 560/172; 560/183; 560/262

[58] **Field of Search** 562/574

[56] **References Cited**

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Primary Examiner—Michael L. Shippen

Attorney, Agent, or Firm—Carolyn D. Moon

[57] **ABSTRACT**

This invention relates to a novel synthesis of 4-amino-5-hexenoic acid by thermal rearrangements, and to the novel intermediates produced thereby.

1 Claim, No Drawings

PROCESS FOR PREPARING 4-AMINO-5-HEXENOIC ACID

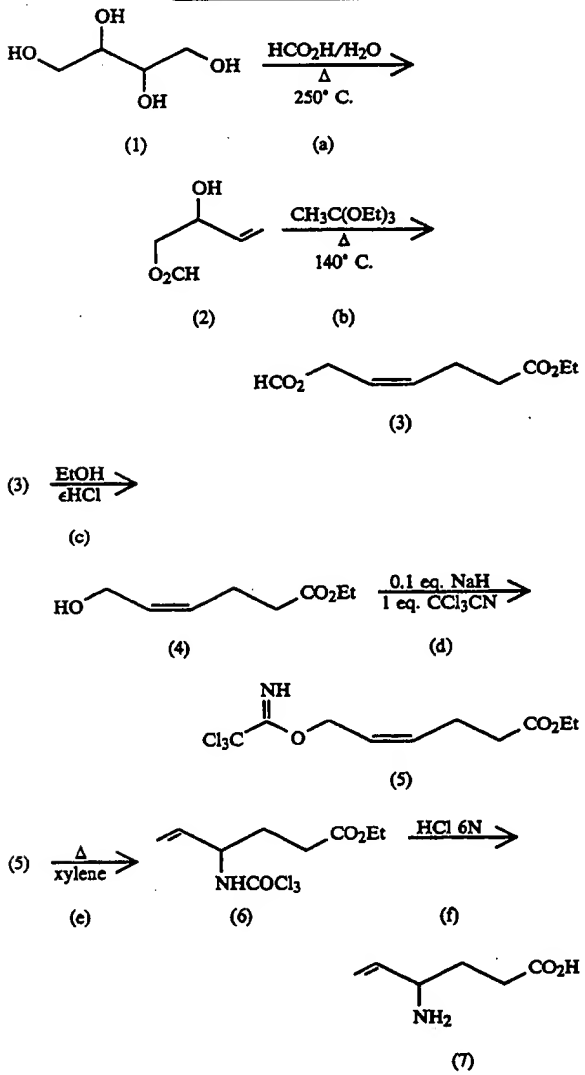
This is a continuation of application Ser. No. 07/986,636, filed Dec. 7, 1992, now abandoned.

This invention relates to a novel synthesis of 4-amino-5-hexenoic acid using thermal rearrangement reactions, and to the novel intermediates produced thereby.

4-Amino-5-hexenoic acid, otherwise known as vigabatrin or vinyl GABA is a GABA-T inhibitor marketed under the tradename SABRIL ® for the treatment of epilepsy. (See *review article on vigabatrin* by S. M. Grant, et al in Drugs, 41 (6):889-926, 1991).

In essence, this process is based upon known thermal reactions starting from erythritol; said thermal reactions being (1) an elimination process for the formation of a double bond, (2) a Claisen rearrangement and (3) an Overman rearrangement. The involved reaction sequence is depicted by the following reaction scheme.

REACTION SCHEME A



wherein Et is ethyl.

Step (a) of the process involves the known thermal rearrangement reaction for the preparation of 4-formyloxy-3-hydroxy-1-butene (2) from erythritol (1) (see Prevost, C., *Ann. Chem.*[10], 10, 398, 1928). Although no work-up is necessary, better yields of a purer compound may be obtained if the product is re-distilled. Step (b) involves a second thermal rearrangement reaction-followed by a hydrolysis-wherein 4-formyl-3-hydroxy-1-butene is heated at 140°–150 ° C. in the presence of excess quantities of the orthoacetate (4 to 1) under conditions for removal of the in situ produced alcohol. (See Johnson W. and Coll, *J. Am. Chem. Soc.* 92, 741, 1970). Following hydrolysis and removal of the excess orthoacetate, the so-produced product ethyl 6-formyloxy-4-hexanoate may be used as is, or it may optionally be subjected to a distillation for purification or it may be subjected to flash chromatography on SiO_2. Alternatively this thermal rearrangement may be effected using one equivalent of the orthoacetate in an inert solvent which boils around 140° to 150° C. (e.g. xylene). The reaction time for these reactions may be monitored by the measurement of the alcohol (methanol or ethanol) which is distilled off.

Step (c)involves the conversion of the formate to its corresponding alcohol by allowing the formate to be stirred at temperatures of about 15° to 25° C. whilst in absolute ethanol to which catalytic quantities of alcoholic HCl gas has been added. Step (d) involves the reaction of trichloroacetonitrile with ethyl 6-hydroxy-4-hexanoate in the presence of catalytic quantities of NaH (≈0.1 equivalent) in an aprotic anhydrous solvent (preferably anhydrous ether) under an inert-gas, preferably nitrogen, at about 0° C. to form an in situ imidate intermediate (5) which, by thermal rearrangement, is converted to ethyl 4-trichloro-acetoamido-5-hexanoate (6); the rearrangement being effected using the techniques of Overman, L. J., *Am. Chem. Soc.* 98, 2901, 1976. The final step involves the hydrolysis of the imidate, preferably by acid hydrolysis but alternatively using basic hydrolysis conditions, to produce the desired 4-amino-hexenoic acid, as its HCl salt. The free acid or other pharmaceutically acceptable salts thereof may be obtained by standard procedures well known in the art.

The advantages of this process may be summarized as follows:

(1) the process does not utilize or form carcinogenic materials, nor are any dangerous reactants or solvents utilized,

(2) the starting material may be prepared from an inexpensive raw material (potato starch),

(3) reaction sequence may be done with only one purification before the final hydrolysis,

(4) a limited number of organic solvents are needed,

(5) the excess of reactants (e.g. trichloroortho-acetate) and solvents (e.g. xylene) may be recovered and re-cyclized,

(6) lack of undesirable by-products,

(7) reactions are facile without problems associated with temperature control and the products may be purified without the need for chromatographic work-up.

The following example illustrates the novel process of this invention.

EXAMPLE 1

4-Amino-5-hexenoic acid

STEP A: 4-FORMYLOXY-3-HYDROXY-1-BUTENE:

A solution of erythritol (50 g, 0.5 mole) in aqueous formic acid (150 g, 75%) was heated above 100° C., 12

H, then water and formic acid were distilled off and the reaction mixture was heated above 200° C. with a Bunsen burner. The product was collected by distillation (b.p. 230° C., 30 g) and should be rectified (b.p. 90° C., 15 mn).

^{1}H NMR (90 MHz) ($CDCl_3$, TMS) δ ppm. 3.23 (s, 1 H, OH), 3.6 (m, 1 H, CH), 4.23 (t, 2 H, CH_2), 5.33 (m, 2 H, CH_2=), 5.83 (m, 1 H, —CH=), 8.16 (s, 1 H, HCO_2).

STEP B: ETHYL 6-FORMYLOXY-4-HEXANOATE:

A solution of 4-formyloxy-3-hydroxy-1-butene (1.06 g, 10 mmol) and propionic acid (1 drop) in triethylorthoacetate (6 g, 40 mmol) was heated at 140° C. under conditions for distillative removal of ethanol. After 2 H, the excess of ethylorthoacetate was removed by distillation in vacuo. The residue was hydrolysed with water and extracted with AcOEt. The product was purified by flash chromatography on SiO_2 (eluant AcOEt: hexane, 2:8) (1 g, 60%) but distillative purification is preferred when larger quantities are involved.

^{1}H NMR (90 MHz) ($CDCl_3$, TMS) δ ppm. 1.26 (t, 3 H, CH_3, J =6 Hz), 2.4 (s, 4 H, $(CH_2)_2$), 4.1 (q, 2 H, CH_2, J =6 Hz), 4.6 (d, 2 H, CH_2—C=, J =6 Hz), 5.73 (m, 2 H, CH=CH), 8.06 (s, 1 H, HCO_2).

STEP C: ETHYL 6-HYDROXY-4-HEXANOATE:

A solution of 6-formyloxy-6-hexanoate (0.9 g, 5 mmol) in absolute EtOH (10 mL) containing few drops of a saturated solution of alcoholic HCL gas was left 2 H at 20° C. The solvent was removed in vacuo and the residue was used for the next step without further purification (0.7 g, quantitative). This compound was found to be partially decomposed by flash chromatography on SiO_2.

^{1}H NMR (90 MHz) ($CDCl_3$, TMS) δ ppm. 1.26 (t, 3 H, CH_3, J =6 Hz), 2.4 (s, 4 H, $(CH_2)_2$), 2.83 (s, 1 H, OH), 4.1 (s, 2 H, CH_2—C=) 4.16 (q, 2 H, CH_3CH_2, J 6 Hz), 5.7 (s, 2 H, CH=CH).

STEP D: ETHYL 4-TRICHLOROACETAMIDO-5-HEXANOATE:

Sodium hydride (0.03 g of a 50% dispersion in oil, 0.5 mmol, was added to a solution of ethyl 6-hydroxy-4-hexanoate (0.7 g, 5 mmol) and trichloroacetonitrile (0.6 g, 5 mmol) in anhydrous ether (50 mL) under N_2 at 0° C. After 1 H, ethanol (0.5 mmol) was added and the solvent was removed in vacuo. The formation of the imidate was controlled by NMR (NH, ~8.5 ppm). A solution of the crude imidate in xylene (30 mL) was heated at reflux 48 H. Then the solvent was removed in vacuo and the residue was purified by flash chromatography on SiO_2. (eluant AcOEt: hexane, 2:8) to give the title product (1.1 g, ~70%). ^{1}H NMR (90 MHz) ($CDCl_3$, TMS) δ ppm. 1.23 (t, 3 H, CH_3, J =6 Hz), 2.0 (t, 2 H, CH_2—CH_2-CO_2, J =5 Hz), 2.36 (s, 2 H, CH_2CO_2), 4.1 (q, 2 H, CH_3CH_2, J =6 Hz), 4.4 (t, 1 H, CH—CH_2, J =5 Hz), 5.1 (m, 2 H, CH_2), 5.76 (m, 1 H, CH=CH_2), 7.2 (s, 1 H, NH). A sample was distilled for analysis (b.p. 150° C., 0.5 mmHg).

Analysis calculated for $C_{10}H_{14}NO_3Cl_3$: C: 39.69 H: 4.66 N: 4.64 Found: C: 39.87 H: 4.62 N: 4.49

STEP E: 4-AMINO-5-HEXENOIC ACID:

A suspension of ethyl 4-trichloroacetoamido-5-hexanoate (0.3 g, 1 mmol) in 6N HCl (10 mL) was heated under reflux 6 H. Then the mixture was concentrated in uacuo, diluted with water (10 mL), washed twice with Acoet, and dried in uacuo to give the title product (0.18 g, 100%). NMR, TLC (NH_4OH:EtOH, 3:7) are identical with those of an authentic sample of 4-amino-5hexenoic acid.

^{1}H NMR (90 MHz) (D_2O), δ ppm. (TMS) 1.83 (m, 2 H, CH_2CO_2), 2.33 (m, 2 H, CH_2CH_2) 3.66 (m, 1 H, CH—C=), 5.35 (m, 3 H, CH_2=CH).

What is claimed is:

1. The process for preparing 4-amino-5-hexenoic acid, or its pharmaceutically acceptable salts thereof which comprises the steps:

(a) thermally rearranging erythritol to 4-formyloxy-3-hydroxy-1-butene, in the presence of an excess of formic acid,

(b) thermally rearranging 4-formyloxy-3-hydroxy-1-butene to ethyl 6-formyloxy-4-hexanoate, followed by the conversion of the formate to its corresponding alcohol ethyl 6-hydroxy-4-hexanoate,

(c) converting the so-produced ethyl 6-hydroxy-4-hexanoate to ethyl 6-trichloroacetimidoxy-4-hexanoate by reaction with trichloroacetonitrile, followed by its thermal rearrangement to ethyl-4-trichloroacetamido-5-hexanoate which, by hydrolysis is converted to the desired 4-amino-5-hexenoic acid, and optionally converting said acid to a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CO CTION

PATENT NO. : **5,380,936**

DATED : **January 10, 1995**

INVENTOR(S) : **Patrick Casara**

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

At Column 2, line 11, the patent reads "4-hexanoate" and should read --4-hexenoate--.

At Column 3, lines 10 and 26, the patent reads "4-HEXANOATE" and should read --4-HEXENOATE--, and in line 27, the patent reads "6-hexanoate" and should read --6-hexenoate.

At Column 3, lines 38-39, the patent reads "J 6 Hz" and should read --J=6 Hz--.

At Column 3, line 41, the patent reads "5-HEXANOATE" and should read --5-HEXENOATE--, and in lines 44-45, the patents reads "4-hexanoate" and should read --4-hexenoate--.

At Column 4, lines 17-18 and 44, the patent reads "5-hexanoate" and should read --5-hexenoate.

At Column 4, lines 20 and 21, the patent reads "uacuo" and should read

At Column 4, Claim 1, lines 37, 39, 40-41, and 41-42, the patent reads "4-hexanoate" and should read --4-hexenoate--.

Signed and Sealed this

Twenty-third Day of July, 1996

Attest:

Bruce Lehman

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

Attachment E

[Record of Maintenance Fees Paid]

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 5487 | ISTMT | DATE PRINTED 10/19/2009

ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,380,936	**$2,020.00**	**$0.00**	**07/02/02**	**08/184,762**	**01/10/95**	**01/19/94**	**08**	**YES**	**M01645AUSA**

Commissioner for Patents
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P.O. Box 1450
Alexandria, VA 22313-1450
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Customer No 5487 | ISTMT | DATE PRINTED 10/19/2009

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,380,936	**$1,050.00**	**$0.00**	**06/30/98**	**08/184,762**	**01/10/95**	**01/19/94**	**04**	**YES**	**M01645AUSA**

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 5487 | ISTMT | DATE PRINTED 10/19/2009

ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,380,936	**$1,900.00**	**$0.00**	**07/10/06**	**08/184,762**	**01/10/95**	**01/19/94**	**12**	**YES**	**M01645AUSA**

Attachment F

[Chronology of Events]

Sabril (vigabatrin) Drug Development History

02/15/80:	Original IND 17,213 submitted to FDA
05/14/80:	IND 17,213 placed on clinical hold by FDA
08/06/81:	Clinical Protocol 97-001 submitted to IND 17,213
09/14/81:	IND 17,213 FDA allowed Clinical Protocol 97-001 to enroll patients
02/18/83:	Clinical Protocol 97-006 submitted to IND 17,213
03/30/83:	IND 17,213 Amendment submitted
07/18/83:	IND 17,213 FDA does not allow any additional patients to be treated with vigabatrin and that current vigabatrin treated patients who do not show marked improvement should be withdrawn from vigabatrin
09/30/83:	IND 17,213 FDA does not allow any additional patients to be treated with vigabatrin
03/07/84:	FDA denies implementation of new clinical study
05/18/84:	Peripheral Central Nervous System Advisory Committee Meeting held (IND 17,213)
06/24/85:	Sponsor/FDA Meeting to discuss current animal testing and foreign human experience
10/18/85:	Peripheral Central Nervous System Advisory Committee Meeting held (IND 17,213)
11/20/85:	FDA puts partial clinical hold on IND 17,213 (no new patients are allowed to be dosed until a validated method to detect early pathological changes in animals is developed)
10/9/86:	Request submitted to IND 17,213 to initiate new clinical studies
01/15/87:	Sponsor/FDA Informal Meeting
012/02/88:	IND 17,213 Amendment submitted (key clinical safety data from Europe)
08/01/89:	Sponsor/FDA Meeting to discuss what material to present at upcoming Peripheral Central Nervous System Advisory Committee Meeting
10/05/89:	Sponsor/FDA Meeting to discuss outstanding nonclinical issues
10/31/89:	Background Document submitted to support 11/20/89 Peripheral Central Nervous System Advisory Committee Meeting
11/20/89:	Peripheral Central Nervous System Advisory Committee Meeting held to discuss the current hold on vigabatrin clinical studies (IND 17,213)
02/26/90:	IND 17,213 Amendment submitted (nonclinical and clinical studies to be used in support of an NDA filing)
04/19/90:	Sponsor/FDA Meeting
07/11/90:	FDA allows continuation of clinical studies and removes IND clinical hold
10/14/92:	Pre-NDA Meeting request submitted to IND 17,213
01/14/93:	Pre-NDA Meeting
04/29/94:	Original CPS NDA 20-427 submitted to FDA
05/05/94:	Case Report Forms submitted to CPS NDA 20-427
08/28/94:	CPS NDA 20-427 4 month Safety Update submitted

Sabril (vigabatrin) Drug Development History

04/28/95:	FDA issues CPS NDA 20-427 Not Approvable Letter
05/23/95:	Sponsor/FDA Meeting to Discuss Not Approvable Ltr
08/04/95:	Sponsor/FDA Meeting to Discuss Not Approvable Ltr
05/29/97:	Submitted CPS NDA 20-427 Amendment (Response to Not Approvable Ltr)
11/26/97:	FDA issues CPS NDA 20-427 FDA Approvable Ltr
12/23/97:	Submitted CPS NDA 20-427 Amendment (Response to Not Approvable Ltr)
01/20/98:	Submitted CPS NDA 20-427 Amendment (Safety Update)
04/24/98:	Submitted CPS NDA 20-427 Amendment (Response to Not Approvable Ltr)
08/27/98:	Sponsor/FDA Meeting to Discuss Visual Field Defects
10/27/98:	FDA issues CPS NDA 20-427 FDA Not Approvable Ltr
02/04/99:	Sponsor/FDA Meeting to Discuss Not Approvable Ltr
04/08/99:	Sponsor/FDA Meeting to Discuss Development Path
03/31/00:	Orphan Drug Application for IS Submitted
06/12/00:	Orphan Drug Application approved for IS by FDA
09/29/00:	CPS NDA 20-427 Amendment Submitted (Proposal for IS indication)
08/09/02:	Sponsor/FDA Meeting to Discuss Development Path for IS indication
06/23/03:	Submitted CPS NDA 20-427 Amendment (Europe Article 12 Update)
06/02/04:	IND 17,213 and CPS NDA 20-427 transferred from Sanofi-Aventis to Ovation Pharmaceuticals
12/01/04:	CPS NDA 20-427/ IS NDA 22-006 Pre-NDA meeting held with FDA
7/27/05:	Submitted to IND 17,213 Pediatric written request for IS
9/27/05:	Submitted to NDA 20-427 (CPS) proposed list of studies for inclusion in suicidality analysis to FDA
9/30/05:	Submitted SABRIL trade name request for conditional approval
10/05/05:	CPS NDA 20-427 / IS 22-006 Pre-NDA telecon held with FDA
12/23/05:	Submitted CPS NDA 20-427 Amendment
2/01/06:	FDA Telecon to discuss deficiencies with CPS NDA 20-427 12/23/05 Amendment
2/14/06:	CPS NDA 20-427 FDA Deficiency ltr received and NDA review clock stopped
10/10/06:	Submitted CPS NDA 20-427 Amendment/Complete Response
10/17/06:	Submitted IS NDA 22-006 Original NDA
11/01/06:	Submitted to CPS NDA 20-427 Suicidality Analysis
11/09/06:	CPS NDA 20-427 FDA Incomplete Response Ltr received
11/09/06:	IS NDA 22-006 FDA Refusal to File Ltr received
12/11/06:	IS NDA 22-006 FDA Incomplete Response Ltr received

Sabril (vigabatrin) Drug Development History

11/22/06:	CPS NDA 20-427 Submitted Corrected Suicidality Analysis
3/01/07:	Submitted CPS NDA 20-427 Amendment/Complete Response
3/08/07:	Submitted IS NDA 22-006 Amendment/Complete Response
4/03/07:	CPS NDA 20-427 Incomplete Response Ltr received from FDA
4/05/07:	IS NDA 22-006 Refusal to File Ltr received from FDA
6/06/07:	CPS NDA 20-427 / IS 22-006 Type A Meeting to discuss MRI abnormalities with FDA
12/28/07:	Submitted CPS NDA 20-427 Amendment/Complete Response
12/28/07:	Submitted IS NDA 22-006 Original NDA
2/26/08:	CPS NDA 20-427 Type 2 Complete Response Accepted by FDA
2/26/08:	IS NDA 22-006 Accepted for Review by FDA
4/25/08:	Submitted CPS NDA 20-427 Request for partial waiver for pediatric development (Birth - 1 month)
4/25/08:	Submitted IS NDA 22-006 4 month Safety Update
6/30/08:	Submitted to CPS NDA 20-427 Pediatric Drug Development Plan/Study Synopsis
10/31/08:	Submitted CPS NDA 20-427 Amendment (Study 1A Clinical Study Report, Safety Update, labeling, Through QT Clinical Study Report)
10/31/08:	Submitted IS NDA 22-006 Amendment (Study 1A Clinical Study Report, labeling)
11/26/08:	Submitted CPS NDA 20-427 / IS 22-006 Amendment [Risk Evaluation & Mitigation Strategy (REMS)]
12/24/08:	Submitted CPS NDA 20-427 Amendment (REMS, labeling)
12/24/08:	Submitted IS NDA 22-006 Amendment (REMS)
01/07/09:	Peripheral Central Nervous System Advisory Committee Meeting held (NDA 20-427)
01/08/09:	Peripheral Central Nervous System Advisory Committee Meeting held (NDA 22-006)
01/30/09:	Submitted CPS NDA 20-427 Amendment (REMS, labeling, drug product stability, Phase 4 clinical studies synopses)
01/30/09:	Submitted IS NDA 22-006 Amendment (REMS, labeling, DP stability, Phase 4 clinical studies synopses)
02/24/09:	Submitted CPS NDA 20-427 Amendment (REMS)
02/24/09:	Submitted IS NDA 22-006 Amendment (REMS)
03/10/09:	Submitted CPS NDA 20-427 / IS NDA 22-006 Amendment (Med Guides, Patient Education Brochures, Dosing Usability, Syringe Durability)
04/03/09:	Submitted to CPS NDA 20-427 proposed CPS labeling based on 3/30/09 FDA proposal
04/09/09:	Submitted CPS NDA 20-427 / IS 22-006 Amendment (REMS) based on April 1 FDA comments
04/24/09:	Submit IS NDA 22-006 CMC Amendment (Cincinnati (CMO)/Anderson Packaging)

Sabril (vigabatrin) Drug Development History

04/30/09:	Submit CPS NDA 20-427 CMC Amendment [Cincinnati (CMO)]
05/22/09:	Submit to IS NDA 22-006 carton/container labels
05/27/09:	Submitted proposed CPS/IS labeling based on 05/21/09 FDA proposal
06/22/09:	Submitted CPS and IS carton/container labels
07/07/09:	Submitted CPS and IS labeling based on 06/24/09 FDA proposal
07/07/09:	Submitted CPS NDA 20-427 / IS NDA 22-006 Amendment (REMS) based on 06/26/09 FDA comments
07/21/09:	Submitted dates for CPS/IS Post Marketing Commitments and Requests
07/27/09:	Submitted revised CPS safety tables to FDA for labeling
08/03/09:	Submitted revised CPS safety tables to FDA for labeling
08/05/09:	Submitted revised CPS efficacy tables to FDA for labeling
0811/09:	Submitted revised anemia study values to FDA for labeling
08/17/09:	Submitted Dr. Appleton financial disclosure statement (IS Study W019 Clinical Investigator) to FDA
08/19/09:	Submitted revised Med Guide to FDA to include their 08/119/08 requested changes
08/19/09:	Submitted final dates to FDA for CPS/IS Post Marketing Commitments and Requests
08/21/09:	FDA approves CPS NDA 20-427 / IS 22-006 NDA

Attachment G

[Certification]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re U.S. Patent No. 5,380,936	)	Patent
Issued: January 10, 1995	)	
To: Commissioner of Patents	)	
Assignee: Lundbeck Inc.	)	
For: Process for Preparing 4-Amino-5-Hexenoic Acid	)	

ATTN: MAIL STOP PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

CERTIFICATION

I, EDWARD P. GAMSON, do hereby certify that this accompanying application for extension of the term of U.S. Patent No. 5,380,936 under 35 U.S.C. § 156, including its attachments and supporting papers, is being submitted as one original and two (two) copies thereof.

Respectfully submitted,

Date: October 19, 2009

Husch Blackwell Sanders Welsh & Katz

By: _____

Edward P. Gamson
Reg. No. 29,381